VOL. XXIII., NO. 12 OCTOBER, 1930.

Medical Library

PROCEEDINGS *of the* ROYAL SOCIETY OF MEDICINE

LONGMANS, GREEN & Co Ltd
39, PATERNOSTER ROW, LONDON
NEW YORK · BOMBAY · CALCUTTA · MADRAS

All rights reserved

Sedare dolorem opus divinum est.
—HIPPOCRATES

The Power of Relieving Pain is a Specific Property of Thermotherapy

Due to its ability to maintain moist heat for a long time

Antiphlogistine

relieves local congestion, and breaks down a vascular stasis. It causes an inhibition of the sensory nerves, thus relieving pain by acting through the thermal nerves of the skin.

Antiphlogistine is an analgesic, depletant and supportant measure for inflammatory conditions associated with pain and discomfort.

Antiphlogistine retains its heat for from twelve to twenty-four hours, thus obviating the necessity for frequent changes occasioned by other forms of poultices.

Write for sample and literature

THE DENVER CHEMICAL MFG. CO.
(Inc. U.S.A. Liability Ltd.)
LONDON, E.3.

You may send me literature and sample of Antiphlogistine for clinical trial.

.....

Address .....

.....

"No one who has seen the relief which follows a good poultice..... ...will ever doubt the value of heat therapy"
—THE LANCET, London.

Section of Dermatology.

[*June* 19, 1930, *continued.*]

Congenital Ichthyosiform Erythroderma or Psoriasis (?). — W. N. GOLDSMITH, M.D.

H. H., a boy, aged 11.

History.—The skin was quite normal till the boy was 12 weeks old, when a red rash appeared on the chest, after the use of camphorated oil, and steadily spread over the whole body. Since that time it has never cleared up except for one year, following X-ray treatment at the London Hospital when he was about 5 years old. Since then the skin has remained more or less in its present condition.

He was first seen by me when already an in-patient at the Prince of Wales Hospital, in May, 1929. The condition had been considered to be psoriasis. Almost the whole of the skin was red and scaly, the most severely involved parts being the chest, back, abdomen and face. The character of the eruption itself, which was very diffuse, with no sharp demarcations anywhere between healthy and diseased areas, rather suggested to me a severe seborrhœic dermatitis. No pityrosporon was found in the scales, but numerous staphylococci were discovered. There was ectropion. The general health was good.

Prolonged treatment with sulphur and salicylic ointment, together with ultra-violet light, brought about considerable improvement, but nowhere did the affected skin really return to normal. Before I saw him he had been treated by arsenic, and later by autogenous vaccine from the fæces, both without benefit. After his discharge from hospital in July, 1929, I did not see him again until May 20, 1930. The skin had then become worse, never having cleared up in the meantime. On this occasion I was particularly struck by the great hyperkeratosis and shagreenation of the wrists, and it was only then that I became aware that his mother had suffered from a similar complaint since the age of 16 or earlier.

Present condition.—The whole of the skin is involved, the least affected part at the moment being the chest. He is better now than he has ever been since the onset. There is a dry ichthyotic hyperkeratosis involving the flexures; over the wrists this is follicular and shagreen-like. The palms and soles are uniformly hyperkeratotic. The lower eyelids are drawn down. His general condition is fair, and he has an abnormally large appetite. Occasionally he has pain and swelling in the knees.

The mother's skin was quite normal until the age of 16, when an eruption appeared on the elbows and knees and steadily spread till every portion of skin was involved to as severe a degree as that in her son's case. It remained continuously bad for five years. After that there was an extreme intensification during each pregnancy, followed by definite improvement, the general tendency during the last eleven years being towards improvement. She is better now than she has been since the first onset, but she states that even four months ago there was not a single

patch of skin unaffected. She has also had ectropion just as bad as her son's; it was at its worst about eight years ago. She has had rheumatic pains. She has now psoriasiform lesions, not sharply demarcated, on the shins, sacrum, arms and scalp; the flexures are free. There is pitting of the nails. The palms and soles are uniformly keratotic, with long fissures.

Comment.—The mother's present appearance strongly suggests psoriasis, but she gives the very definite history that her condition has been exactly the same as that of her son, in whose case I should hesitate to make that diagnosis, in view of the early onset, intensity, persistence and universality of the eruption, the ectropion, the shagreenation in the flexures, and the smooth hyperkeratosis of the palms. Further, his condition was practically uninfluenced by a long stay in hospita with daily inunctions and ultra-violet radiation. On the other hand, it is difficult to label the mother's condition "*congenital* ichthyosiform erythroderma," as the onset was not until the age of 16 years. Possibly this disease may manifest itself late in some cases, just as "keratosis palmaris et plantaris hereditaria" and all kinds of nævi may do. Even at present, the type of hyperkeratosis on her palms, which have been hard since childhood, is unlike psoriasis. It is particularly interesting to note her assertion that she once had ectropion to the same extent as her son now has, and that this has completely disappeared. There appears to be a definite endocrine element in her case, judging from the fact that the onset was soon after puberty, and that there were intensifications, followed by improvements with each pregnancy.

Discussion.—Dr. H. C. SEMON suggested, as an alternative diagnosis, that this might be psoriasis in an ichthyotic subject. He presumed there was no reason why an ichthyotic subject should not have psoriasis.

Dr. H. W. BARBER said that he thought the condition in both mother and child was pityriasis rubra pilaris. In his experience this disease usually followed one of three courses: (1) After beginning like psoriasis—but soon showing the characteristic follicular hyperkeratosis and the involvement of the palms and soles—it became a generalized erythrodermia, often with ectropion, which ran a course of some months or years, the whole skin eventually recovering completely. Subsequent and similar attacks might occur. (2) The erythrodermia might partially disappear, leaving the palms and soles affected. (3) It might persist indefinitely. No treatment appeared to have any influence on the disease.

Dr. GOLDSMITH (in reply) said he was not aware that in pityriasis rubra pilaris there would be such flat, lamellar, crocodile-like scaling as was present on the arms in this boy's case.

Congenital Ichthyosiform Erythrodermia.—H. W. BARBER, M.B.

J. T., a girl, aged 4. This is a characteristic example of the condition labelled by Unna "congenital hyperkeratosis," and by Brocq "congenital ichthyosiform erythrodermia." The family history is of some interest. The child is the elder of two girls, and there is asthma on the mother's side of the family and eczema on the father's side. The mother herself has ordinary ichthyosis. The child developed asthma after measles.

When she was born the entire skin was affected, but as she grew older certain areas became normal, these areas corresponding to the parts exposed to light. At the present time the characteristic scaliness involves the trunk, the scalp, forehead and posterior part of neck, axillæ, flexor surfaces of upper arms, antecubital fossæ, upper parts of thighs, and the palms (slightly). There is some ectropion, but the lower part of the face, the anterior part of the neck, the extensor surfaces of the arms below the deltoid region, and the legs, below the cut of the drawers, are free.

The marked involvement of the flexures in this condition suffices to differentiate it from ordinary ichthyosis, and, of course, the histology is quite different. It is, however, interesting that the mother has ordinary ichthyosis, and that there is a personal and family history of asthma.

I have asked the mother to allow the child to have total sun baths later in the summer in order to see whether the whole skin will return to normal if exposed to light and air.

Pustular Psoriasis.—H. W. BARBER, M.B.

F. R., male, aged 29; bath attendant.

History.—The hands were first affected four years ago, but recovered to a great extent until a relapse occurred about six months ago, at which time the feet also became involved. The patches on the knees and the changes in the nails appeared about three months ago.

I am showing the case in support of the contention that the condition described by Dr. Dore [1] in January, 1928, as a "chronic, mild, localized type of acrodermatitis perstans," of which Dr. Roxburgh [2] showed two cases in October, 1927, is really a pustular form of psoriasis. The whole question will be discussed in detail at the next meeting of the British Association of Dermatology and Syphilology.

This patient presents symmetrical scaly patches on the palms, involving chiefly the thenar eminences. In these patches arise intra-epidermic pustules, which dry to form brownish scabs; the palmar surfaces of the fingers are also to some extent affected. Similar patches are present on the soles over the insteps, particularly on the left foot. There are symmetrical scaly patches on the knees, which appear to be ordinary psoriasis, and the nails, particularly those of the thumbs, present changes—pitting and scaliness of the nail-beds—suggestive of this disease, and entirely different from those seen in true acrodermatitis. Examination of scrapings and cultures has been negative, not only for fungus, but also for micro-organisms. This is the rule in these cases, and cultures from actual pustules may be sterile, not even the ordinary *Staphylococcus albus* growing. I would particularly emphasize the distribution of these symmetrical pustular patches: on the palms, the thenar eminences, and on the soles, the inner surfaces of the insteps are the sites of election.

I had hoped to show a similar case at the last meeting, and I have a patient under my care who for years has suffered from ordinary severe psoriasis. Recently the pustular patches on the palms and soles have developed chiefly on the sites of election indicated above, the pustule formation being very severe.

[1] DORE, S. E., *Brit. Journ. Derm. and Syph.*, 1928, xl, 12. [2] ROXBURGH, A. C.; *ibid.*, 27.

Urticaria Pigmentosa.—G. B. DOWLING, M.D.

Patient, male, aged 23.

A month ago presented red urticarial lesions, of generalized distribution, with isolated bullæ and many scars from old bullæ.

So far as he knows he has had the condition from earliest infancy. In the first years it was irritable, but for a long while no irritation or other symptoms have been associated with it. Some of the bullæ have become pustular and have ulcerated and left scars. To-day there are groups of vesicles and bullæ, especially on the back and arms, and the grouped appearance suggests dermatitis herpetiformis rather than my original diagnosis of urticaria pigmentosa, but if it is dermatitis herpetiformis the total absence of irritation is remarkable.

Ulerythema ophryogenes (Unna).—G. B. DOWLING, M.D.

Patient, female, aged 5 years.

The condition has been present practically since birth. First, lack of eyebrows was noted, then erythema. There is slight irritation present.

Present Appearance.—Erythema on eyebrows, forehead, between eyes, and pre-auricular area of face. Minute, closely set, perifollicular warty elevation throughout affected area. Hair sparse.

Dr. A. M. H. GRAY said that Dr. Dowling's first case was very interesting. After seeing the condition to-day he did not think it would be possible any longer to maintain that it was urticaria pigmentosa; he did not think crops of herpetic-like vesicles occurred in urticaria pigmentosa, nor did he think the patches of pigment were permanent. Clinically, the condition seemed like dermatitis herpetiformis; he was however surprised at the absence of itching. It was true one saw cases of the dermatitis herpetiformis which had no itching, but that was particularly so when the bullæ were large. When the lesions were small they usually itched.

Pityriasis Lichenoides et Varioliformis Acuta.—W. KNOWSLEY SIBLEY, M.D.

V. W., female, aged 36, came to St. John's Hospital for Diseases of the Skin, May 29, 1930, complaining of a rash which had been "coming out" for one week and was accompanied by violent irritation. It had begun with general pains, some headache, sore throat, and vomiting, with a slight rise of temperature. Two days before she came to hospital she had been seen by several doctors, including the medical officer of health, who sent her in an ambulance to the South Wharf, Rotherhithe, Smallpox Hospital. She had then neither temperature nor pain, and

Dr. Knowsley Sibley's case.

was put into the observation ward, from which she was discharged next day. The forearms, especially the posterior surfaces, were extensively covered by a papular—and, in places, small vesicular—rash, which was very hard and shotty to the touch; several papules showed umbilication, with evidence of scratching. A few similar lesions were coming out about the knee, lower calves, and body, but none on the face or neck. Her mouth was generally uncomfortable, and painful, and there were

several minute ulcers on the tongue, which was furred, while the naso-pharynx was generally congested.

June 2, 1930.—There was a marked regression.

Histological Report by Dr. I. Muende.—The epidermis shows slight acanthosis, with intra- and inter-epithelial œdema, associated with some leucocytic infiltration.

The small blood-vessels of the papillary bodies are very dilated and exhibit swelling of the lining endothelium, together with marked perivascular cellular infiltration. The connective tissue, particularly in these regions, is very œdematous. The cellular infiltration is composed chiefly of lymphocytes, only about 10% being polymorphonuclear. The von Pirquet and Wassermann reactions are negative.

Dr. A. H. M. GRAY said he would have thought that everything in this case was against the diagnosis of pityriasis lichenoides acuta. In pityriasis lichenoides the rash was much more abundant on the trunk than on any other part of the body. In the present case the trunk was largely free. Secondly, the rash had disappeared in a very short time; and, thirdly, Dr. Sibley was certain that the lesions were primarily vesicular. The lesions in pityriasis lichenoides acuta were essentially slightly raised macules or papules, and the only time when there was an appearance like a vesicle was when necrosis occurred; they were never truly vesicular, and further, he did not think that they had ever been described as occurring in the mouth.

Urticaria Pigmentosa (Macular Type).—RIPLEY ODDIE, M.B., B.Ch.

Leslie B., aged 8. Lesions first noticed at age of 3 months, appearing first on the temple. Rapid increase up to age of 9 months, since when the condition has been more or less stationary, with periodic occurrence of new spots.

Areas are at first yellowish-pink, becoming fully pigmented in two years' time. The tendency to urticate is variable; scratching and heat cause the formation of wheals, which persist up to three days. Swelling is not marked. There have been long periods of quiescence.

Patient was never vaccinated. Had chickenpox at age of 4 years and measles at age of 5; neither influenced the course of the disease.

Numerous pigmented and roughened macules on face, neck, scalp margin and trunk. No glandular swelling, no dermographism.

Bleeding time, 1 min.; coagulation time, 2 min. 8 sec.; blood calcium, 10·3 mg. per 100 c.c.; fragility of R.B.C. slightly lowered; platelet count 275,000 per c.mm.

Biopsy.—Three sections, stained with hæmalum and eosin, carbolthionin and orcein. These show (1) flattening of papillæ, (2) hyper-pigmentation in basal layer, (3) a collection of large mononuclear, granular and non-granular cells occupying the corium. No mast cells were found.

The PRESIDENT said that this case had been shown by Dr. MacLeod in 1923,[1] but there was no previous record of a microscopical examination having been made.

With regard to the apparent absence of mast cells, Dr. MacLeod was of opinion that these might be found by a different technique in cutting and staining the sections.

Nævus Unius Lateris.—R. T. BRAIN, M.D.

F. M., male, aged 24, attended Dr. W. J. O'Donovan's clinic on account of a linear ulcer, six inches long, on the left shin, of three months' duration. It was regarded as an artefact and completely healed after four weeks' treatment in hospital with simple occlusive dressings. The patient was found to have a remarkable and extensive nævus strictly limited to the left side of the body. It was polymorphic and consisted of macules, slightly raised, flat-topped papules, and warty nodules,

1 *Proceedings*, 1923, xvi (Sect. Derm., 73).

aggregated into areas corresponding closely to the sensory areas of certain segments of the spinal cord. All the lesions were brown in colour, the shade varying from a pale to a very dark tint.

Distribution.—The lesions were found on the left arm, the left side of the trunk and on the left leg, and their distribution corresponded to the following segments of the spinal cord :—

Cervical VII and VIII.—A thickened translucent horny plaque covered the ulnar side of the palm and was continued along the inner two fingers and a half.

Thoracic I and II.—A faint brown macular streak ran along the inner side of the whole arm to the anterior axillary fold.

Dr. R. T. Brain's case of nævus unius lateris.

Thoracic III to VI.—The entire areas on the front of the chest were covered by dark brown warty skin, with a few large plugged sebaceous follicles in the upper part. The lesions became flatter and paler at the side and faded out before reaching the mid-line of the back. A dark linear streak replaced the linea alba.

Thoracic X.—This segmented area was almost completely covered by dark, warty skin.

Lumbar III and IV.—A few brown flat papules were grouped on the inner side of the left knee.

Dr. R. T. Brain's case of nævus unius lateris.

Sacral I.—Small patches of pigmented and warty skin were present below the internal malleolus and at the base of the big toe.

Sacral II and III.—The whole of the left side of the scrotum was dotted with warty papules.

Leukæmia Cutis.—A. M. H. GRAY, C.B.E., M.D.

Patient, male, aged 36. About six months ago he noticed a dark nodule on his left cheek; a little later one appeared on the right cheek, and since then several more have come out on the cheeks, forehead, trunk and limbs. At the present time there are about twenty nodules present; the largest on the cheeks are the size of large cherries, deeply infiltrated, and of a dark plum colour. The surface of the tumours is smooth and shiny. The glands in the groins and axillæ and the epitrochlear glands are slightly enlarged; those in the neck not noticeably affected. Nothing abnormal can be made out in the chest or abdomen; neither liver nor spleen can be felt. X-ray examination of chest showed shadows suggesting enlarged glands at the root of both lungs.

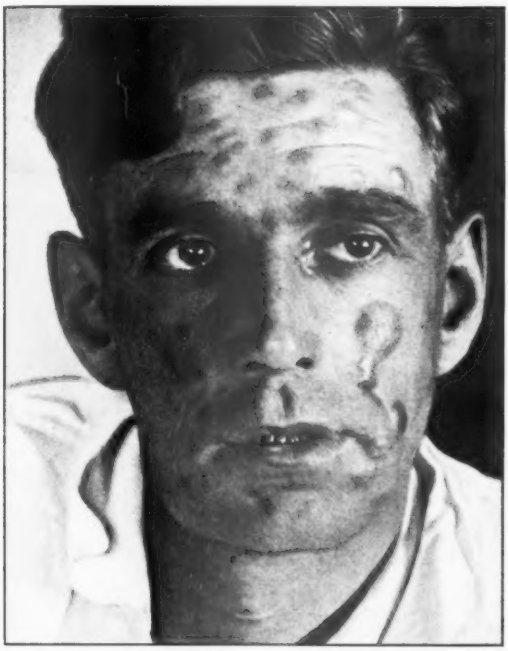
Mr. Herbert Tilley reports that the anterior end of the right inferior turbinate is dusky, congested and granular and that a similar condition is present on the septum opposite. The tonsils are swollen and grey-blue in colour. The larynx and pharynx are normal.

Examination of Blood (Dr. Goodhart).—R.C., 4,540,000 per c.mm.; Hb., 90%; C.I., 1·0; W.C., 5,500 per c.mm. *Differential:* Neutrophil myelocytes, 3%; polys., 46·5%; eos., 3·5%: basos., —; large monos., 1·5%; lymphos., 24%: myelos., 21·5%. Normoblasts, 50 per c.mm. A few red cells show polychromasia and punctate basophilia.

The Wassermann reaction was negative.

Sections have been taken from early and advanced lesions and examined by Mr. W. G. Barnard. They show diffuse, though rather patchy, infiltration of the

dermis and hypoderm. This is most marked along the blood-vessels and around the hair follicles and sweat-glands. It consists of large and small lymphocytes and plasma cells, but in addition there are a few histiocytes, polymorphonuclear leucocytes, and an occasional eosinophil cell. In the deeper parts of the more



Dr. A. M. H. Gray's case of leukæmia cutis.

advanced lesions are numerous small and large lymphocytes arranged in rounded groups, these groups resembling lymphadenoid tissue.

The clinical appearance of the lesions suggested a leukæmia of the skin and this appears to be borne out by the sections and the blood examination.

Discussion.—Dr. H. W. BARBER said he recalled a case in which the patient had typical plum-coloured nodules all over his body, but in which the number of leucocytes in the blood was normal. It was not until shortly before death that the blood-count showed leukæmic changes.

Dr. H. C. SEMON said he gathered that the biopsy showed lymphocytic invasion of the skin and that the blood-count was of the myelocytic variety. Presumably then, this case was of the mixed-celled type, which was referred to by Professor Robert Muir in his article on leukæmia (Allbutt and Rolleston, "System of Medicine," vol. v, p. 792).

Dr. GRAY (in reply) said that this patient had had chronic gastric trouble for two years, but was not very ill. He was going downhill, but quite slowly. In answer to Dr. Semon, he thought the sections would need to be re-stained. The myeloblasts in the blood had been mistaken for lymphocytes, and the sections had not been stained from that point of view. There had not been time to re-stain them before the meeting was held.

Self-mutilation of the Face in a Male.—J. H. T. DAVIES, M.B.

This patient for thirty years has been a tram-driver. In 1908 he had a carbuncle at the back of his neck and he dates the present condition from then. Since 1911 he has lived in Brighton and has had numerous recurrences. He was rejected for war service. I saw him for the first time in 1926, and, not suspecting artefact at first, I made thorough investigations, including microscopic sections. Eventually I came to the conclusion that the lesion was an artefact, and wrote to this effect to the patient's doctor, who then told me that he had formed the same opinion, but had purposely withheld it from me. The doctor told me that the patient never made himself a nuisance at the club, had always been anxious not to trespass on the doctor's time, and was a thoroughly agreeable patient. Recently, however, he consulted his doctor's new partner, who promptly made the diagnosis of tuberculosis, and he is now, I believe, obtaining some quite substantial benefit at the expense of the taxpayer.

On the right side of the face and extending into the scalp is a lesion two inches and a half wide at its upper end, and an inch and a half wide at its lower end, and six inches long, with sharply-cut edges and a clean, granulating floor. It looks just as if a strip of skin had been outlined with a sharp knife and then forcibly peeled off. The face is "decorated" with a symmetrical arrangement of linear scars representing previous ulcerations, which, on the occasions when I have seen them, had the same characteristics as the present one. There are a number of pustules scattered about the old scars.

On this last occasion, however, an ecthyma-like lesion has developed on the outer side of the right leg. The patient associates this with the condition on his face, but it looks to me quite different.

Discussion.—Dr. DOWLING said that this case reminded him of one which Dr. Wigley, Dr. Roxburgh and himself had seen some time ago. The patient was a prisoner who had for some years been at Wormwood Scrubs. He had had exactly the same condition as that in Dr. Davies' case, the appearance suggesting that the skin had been stripped off.

Dr. WIGLEY said that the man to whom Dr. Dowling had referred was now in St. Bartholomew's Hospital, and the condition was unchanged.

"White Spot Disease."—E. G. GRAHAM LITTLE, M.D.

The patient, a woman, aged 24, has a number of atrophic small patches ("white spots") scattered irregularly over the body. The history is that these patches appeared without any previous lesion having occurred; the average size is $\frac{1}{8}$ in. to $\frac{1}{4}$ in., and there are no subjective symptoms in connection with them. She gives a history of recent gonorrhœa, but there is no other constitutional illness and she appears to be otherwise healthy.

Urticaria Pigmentosa Nodulosa.—E. G. GRAHAM LITTLE, M.D.

Patient, a girl, aged 3. The eruption is said to have come on in early infancy and the nodules have greatly increased in number. They are about one-quarter inch in diameter, of a buff yellow colour, causing no subjective sensations, but readily becoming red and turgid upon friction. A section from one of these nodules shows a typical infiltration of the pars papillaris with mast cells.

Extensive Cicatricial Alopecia of Scalp. ? Lichen Planus.—E. G. GRAHAM LITTLE, M.D.

Patient, female, aged 50. The condition dates from 1927. At the edge of the bald areas there is still some follicular inflammation present, but there has been no active suppuration at any time. There are no lesions elsewhere upon the skin, but

there is a curious condition of the tongue. The whole of the surface is occupied by exaggerated white papillæ and the tongue is so tender as to give pain in mastication, and exhibits a tendency to bleed. This symptom has persisted for a considerable time. There is no evidence of lichen planus upon the buccal mucosa, and the appearance of the tongue does not altogether suggest lichen planus, the whitening being too universal to support that diagnosis. The patient has been under the care of one of my colleagues on account of osteo-arthritis, for many years.

Section of Obstetrics and Gynæcology.

[*June* 20, 1930.]

Puerperal Infection by Pathogenic Anaerobic Bacteria.

By A. J. Wrigley, M.D., F.R.C.S.

The literature contains records of an enormous amount of work on uterine infection with the pathogenic anaerobic bacteria, following abortion, though only twenty cases of puerperal infection were discovered after the most prolonged search. As it seemed possible that these cases were more common, the records of the Obstetrical Department of St. Thomas's Hospital were consulted. In the years 1922-1927, sixteen deaths from puerperal sepsis occurred, and of these, in six instances, post-mortem examination revealed that generalized gas gangrene was present. This proportion may, or may not, be abnormally high; it is hoped that observations will be forthcoming on the point.

Though the condition of gas gangrene had been recognized for many years, it was not until 1891 that Welch first isolated the organism, thereafter to be known by his and many other names. Shortly afterwards Fränkel described the same organism under the name of the *Bacillus aerogenes capsulatus* and according to prevalent custom it will be so termed in this paper.

In the work under consideration, attention has been devoted entirely to the part played by this organism. Though it was fully recognized that the members of the same group might be present in certain cases, the *B. aerogenes capsulatus* was by far the most common and the most easily recognized of the pathogenic anaerobes in all the cases examined. No evidence was found of other pathogenic anaerobes in these cases.

Incidence.—The *Bacillus aerogenes capsulatus* has been isolated from many situations, as for example the soil, sewage, water, and food—such as fish and milk. In the human body it has been found in the skin, in the mouth, in the bile and in the urine. It is probably a constant inhabitant of the intestinal canal from early childhood, and in consequence may be found on the skin of the perinæum and around the anus. As regards the bacteriology of the vagina in the pregnant and non-pregnant state, a review of the literature will be published later. It will be sufficient to state at this point that a large amount of work has been done and that the results are, on the whole, fairly uniform. No evidence is forthcoming that *B. aerogenes capsulatus*, or allied organisms, are to be found in the upper part of the vagina, or in the cervical canal. At the same time it must be pointed out that unless specifically sought for, it is likely that this organism would be missed, and again, that by far the greater number of bacterial investigations were, in the past, confined to aerobic cultures. Therefore, the first investigation to be performed was that of the bacteriology of the cervical canal, or what was left of it, at the beginning of labour. Specimens were taken from some fifty cases, and as the technique employed was the same as that used in the puerperium for the examinations of the lochia, it may well be described at this point.

The Technique.—A large sterilized Fergusson's speculum was inserted into the vagina and the cervix was well exposed. A long (7 in.) blunt-ended glass pipette with a slight curve at the end was then passed into the cervix for about 1 in. The pipette was sterilized and had a plug of wool at the teat end. A rubber teat, for purposes of suction, was used. Unless the lochia are abnormally scanty there is no difficulty in obtaining ½ c.c. to 1 c.c. of material with which to work. It was assumed that the inside of the pipette did not become infected during its passage through the cervical canal, and that the material obtained was that from the

interior of the uterus. This material was then expelled from the pipette into a sterile test-tube, or, if the quality was small, the pipette was rinsed with sterile saline.

The technique employed in the examination of placental and fœtal tissues will not be detailed here. All material was cultured aerobically and anaerobically, and although interesting observations could be made on the incidence of many organisms, this paper will be confined as far as possible to the incidence of the pathogenic anaerobic bacteria, more especially the *B. aerogenes capsulatus*.

The result of examination of the contents of the cervical canal at the beginning of labour in fifty women is that *B. aerogenes capsulatus* was not isolated, nor, so far as that goes, was its presence even suspected from inspection of the direct smears in one single instance. It may here be said that this result was contrary to expectation.

Attention was next directed to the incidence of these bacteria in the lochia of normal cases after delivery. Here again, a prolonged search through the enormous amount of literature on the bacteriology of the puerperal uterus proved fruitless. One or two workers had reported the finding of the *B. aerogenes capsulatus* in a few isolated instances out of—generally—several hundreds of investigations, but the proof as to the nature of the organism was usually not given or depended only upon microscopical appearances. No work could be discovered directed primarily to the investigation of the incidence of the bacteria in the lochia. The lochia was examined therefore in one hundred cases in which pregnancy, labour and the puerperium were normal.

Specimens were taken in all these cases upon two occasions, about the second and the sixth days following delivery, and in many instances a third specimen was obtained about the ninth day. Thus, in all, about two hundred and fifty specimens of lochia in such cases were examined. On no occasion was the *B. aerogenes capsulatus* seen or isolated.

From the evidence obtained from the literature and from the above investigations, the conclusion reached at this point is that *B. aerogenes capsulatus* is not present in the cervix before, or in the lochia following, delivery, in cases in which pregnancy, labour and the puerperium are normal, or as some would say physiological. A corollary to this statement would be that, therefore, when the infection does occur, the organisms have been introduced from without, as a result of manipulations or examinations.

Is then the *Bacillus aerogenes capsulatus*, so constant an inhabitant of the rectum, and almost certainly of the perinæum, to be found in the lochia in all those cases in which there has been interference with labour, followed perhaps by uterine infection? The answer is in the negative.

About sixty-nine cases were investigated over this period in which pregnancy, labour or the puerperium was abnormal. The *B. aerogenes capsulatus* was isolated from the lochia in thirteen cases of this series.

Now of these thirteen, four cases fall into a group which includes nearly all those reported in the literature. This type of case is not frequently met with, is often reported in the medical press as a rarity, and in consequence is generally recognized as an entity. The group, in fact, is composed of cases in which the puerperium was complicated by generalized "gas infection" or "gas gangrene." Recovery in these cases appears to be rare and not to be expected—that is, in the unlikely event of a correct diagnosis being made before death. In all these four cases the *B. aerogenes capsulatus* was isolated from the fœtal and placental tissues, in which it was present in large numbers. In addition the organisms were present in the lochia until either death occurred or the patient recovered. In all the cases of this nature gross intra-uterine manipulations had occurred, but in the small series of sixty-nine cases investigated there were sixteen other instances in which similar and somewhat violent efforts made to deliver the child had not been followed by uterine infection with pathogenic anaerobic bacteria.

It appears therefore that for this type of infection to occur, the stage must be set in a definite way. Both in the cases reported in the literature, and in the four of the present series which have been grouped with them, the fœtus had been dead for some hours *in utero*. This is considered to be an important point. Furthermore, in the majority of cases, it is probable that the death of the fœtus corresponded with the manipulative interference, frequently unavailing, to effect delivery, by which the contamination was introduced. Again, it is well known that *B. aerogenes capsulatus* and allied organisms thrive on dead and damaged tissue, and more especially on dead or damaged muscle. The assumption is therefore made that for severe maternal infection with these organisms to occur, the following conditions must be fulfilled in the great majority of cases:—

(1) The organisms must be introduced into the uterus. (2) The organisms must there find suitable material, namely, dead tissue, on which to grow. (3) This culture chamber, the dead fœtus, should remain in the uterus for a sufficient length of time. (4) Damaged maternal tissues should be exposed to the infection provided in this manner.

These points will now be considered in turn.

(1) Intra-uterine manipulations must take place for the introduction of the bacteria. Now, every woman in whom delivery is effected by this means does not suffer from a subsequent generalized gas infection. The reason is that a suitable site for inoculation of the organisms is not provided. In this series of cases, for example, many instances of forceps delivery were investigated in which the pathogenic anaerobic bacteria were not isolated.

(2) The child must be dead at the time of the introduction of infection, or, in other words, at the time of the intra-uterine manipulations, and thereby provide suitable material for growth of these bacteria. Now, if the child is delivered at once, obviously no time is allowed for incubation of the organisms on the dead fœtal tissues. Again, in the series of cases there are instances in which delivery of a stillborn fœtus was effected after interference for relief of fœtal distress. The findings were negative in all these cases as regards the presence of *B. aerogenes capsulatus* and allied organisms in the lochia. Hence the third stipulation.

(3) The child must remain dead *in utero* for some hours following the initial intra-uterine manipulations. In other words, as the organisms have been introduced into the uterus—a suitable culture chamber—and the dead fœtus has been inoculated, if the fœtus remains undelivered, and is therefore kept at body temperature, an extremely rapid proliferation of these organisms is likely to occur.

(4) The original manipulations must have damaged the uterus or birth canal. Should this damage not occur, a suitable site for inoculation of the maternal tissues with the enormous numbers of pathogenic anaerobic bacteria by this time present in the uterus, may not be provided. Thus it will be demonstrated later that if intra-uterine manipulations have not been accompanied by damage to the uterus or birth canal, gross infection of the contents of the uterus may occur without any evidence that the organisms have gained entry to the maternal tissues.

Should any link in the above chain be absent, it appears to be unlikely that generalized gas gangrene will occur. In other words, for a blood-stream infection with *B. aerogenes capsulatus* to supervene there should be present an adequate degree of infection, which is met by a much depleted local or general resistance. These conditions are, of course, common to any infective process, but it is held that a somewhat special set of circumstances is necessary for the production of the adequate infection, and for the lowering of the local maternal resistance to this infection. At the same time it must be emphasized that the worst type of infection may follow trivial interference. In these cases the virulence of the organism, or the lowered general resistance of the patient, would prove to be the deciding factor.

The second group of cases—also four in number—in which the *B. aerogenes capsulatus* was discovered were slightly different in nature, but the factors underlying the infection were identical with those just described. In these cases manipulations were of such a nature that, although the child was dead *in utero*, little damage was thought to be done to maternal tissues at any time and delivery of the child was easy. In these cases the patients survived, though puerperal infection was present. The *B. aerogenes capsulatus* was found in the lochial discharges for many days after delivery. In the first case, that of a woman sent to hospital, the doctor had failed to effect delivery two hours previously. The fœtal heart was not heard, and the cord was prolapsed and not pulsating. As the head was well down in the pelvis and the os not fully dilated, morphine was administered. Natural delivery occurred six hours later. *B. aerogenes capsulatus* was isolated from the fœtus and the placenta, and from the lochia during the puerperium. Clinically the puerperium was normal. The second case was one of placenta prævia. When the os was barely three-fingers' breadth dilated, bipolar podalic version had been performed. After this manipulation the fœtal heart was never heard. Delivery was easy and occurred ten hours later. The placental and fœtal tissues were examined after delivery, and large numbers of *B. aerogenes capsulatus* were discovered in the placental tissues. These organisms were present in the lochia for seven days after delivery. Thirteen examinations were made. Clinically the puerperium was normal. A prophylactic dose of antitoxic serum was given a few hours after delivery.

The third case was one in which labour lasted for forty-two hours. Eighteen hours before delivery the membranes ruptured and the cord prolapsed. Many manipulations were made to replace it. The cord was not pulsating and the fœtal heart was never heard afterwards. Eventual delivery of the child was unaided. Bacteriological examination of the placental tissues showed the presence of large numbers of *B. aerogenes capsulatus*. This organism was not found in the fœtal tissues. The lochia was examined on five occasions and *B. aerogenes capsulatus* was found in decreasing numbers. Other organisms were present. The puerperium was clinically normal. A prophylactic dose of antitoxic serum was given. The fourth case was that of a woman admitted to hospital after having been in labour for three days. The breech presented and the legs were extended. It was thought that the child had been dead for some time. As few manipulations as possible were performed and the child was delivered by gentle, though prolonged, traction with a blunt hook. The child was emphysematous owing to the enormous "gas infection" that had occurred. Both fœtal and placental tissues showed gross invasion by *B. aerogenes capsulatus*. These organisms were present in the lochia in decreasing numbers until discharge from hospital three weeks later. The puerperium was complicated by slow involution and low pyrexia. The patient was treated with antitoxic serum, four doses being administered, until it was obvious that the infection was localized, slight, and decreasing in intensity.

The next case in the series is of great interest as an example of the entry of *B. aerogenes capsulatus* into the blood-stream, possibly as a result of the lowering of the mother's resistance to infection.

The woman, a primipara, was admitted to hospital suffering from eclampsia. Treatment was entirely by means of morphine and chloral hydrate for five days, after which the patient's condition was considered to be sufficiently improved for induction of premature labour to be justified. The fœtal heart had been heard for two days following admission, but neither had the fœtal heart been heard, nor fœtal movements felt during the following three days. It was concluded, therefore, that the fœtus was dead *in utero*. Labour rapidly followed the introduction of bougies. The fœtus was macerated. The *B. aerogenes capsulatus* was isolated from the fœtal and the placental tissues. The patient died six hours after delivery of the fœtus. Smears and cultures from the maternal heart blood made directly after death, showed the presence of *B. aerogenes capsulatus*. These organisms

were demonstrated in all the maternal organs after post-mortem examination. The death was thought to have resulted from eclampsia, although no hæmorrhages had been found within the cranium nor were the changes in the kidneys and liver as extensive as was expected. It would not require great courage to maintain that the cause of death in this case was septicæmia, due to infection by *B. aerogenes capsulatus* occurring in an eclamptic patient. The organisms had almost certainly been introduced at induction of labour; they had multiplied in an ovum, the death of which had been caused by the toxæmia in the mother, and it is suggested that the entrance of the bacteria into the maternal tissues was not as a result of local tissue damage, but a consequence of the extreme lack of resistance on the part of the mother. Recognition of the existence of this type of case is of great importance and will be referred to later.

In the remaining four cases from which the pathogenic anaerobic bacteria were isolated, delivery was easy. In all these cases, bougies were introduced for the production of labour, and further, there was adequate evidence that the fœtus was dead at the time of introduction of the bougies. Thus, in one case, the child was thought to have been dead *in utero* for five days, in two others for four days, and in another for three days. Delivery in all these cases was straightforward and the puerperium was clinically normal. Bacteriological examination showed the presence of *B. aerogenes capsulatus* in the placental tissues, in the fœtal tissues in two instances, and in the lochia for several days following delivery. There was no general or local evidence of maternal infection with these organisms.

At the same time, in the series of cases investigated, there were many other instances in which (1) a stillborn child or macerated fœtus was delivered (but in these cases there were no preceding intra-uterine manipulations), or (2) induction of labour was performed and was followed by the delivery of a live infant. In none of these cases was the *B. aerogenes capsulatus* isolated at any time.

Types of Infection.—With regard to the type of infection caused by the pathogenic anaerobic bacteria in the puerperium: so far as can be ascertained, *B. aerogenes capsulatus* is at present barely taken into account at all as a cause of puerperal sepsis, and when it is recognized, either the part which it plays is assumed to be the production of generalized gas gangrene on occasions rare enough to deserve mention in the medical press, or, as stated, in "Midwifery, by Ten Teachers":—

> From the putrid-smelling discharge which characterizes many cases of puerperal fever (sapræmia) anaerobic organisms can indeed be not infrequently isolated, but they represent merely a secondary infection, having little or no influence on the course of the disease.

This statement will first be dismissed. In the series of cases investigated, local uterine sepsis, once known as "sapræmia," was present in thirty-one instances, and was accompanied by the usual "putrid-smelling discharge." In view of the above statement, special search was made for *B. aerogenes capsulatus* in the lochia of these cases, and in not one examination in any case was the organism isolated. A coarse Gram-positive staphylococcus seemed to be the most constant organism present in such lochia, frequently accompanied by a non-hæmolytic streptococcus, *B. coli*, or *Staphylococcus aureus*. It is therefore as erroneous to state that the pathogenic anaerobic bacteria are to be found in the lochia of these cases as it is to state that they represent "merely a secondary infection." It is far more probable that the widely recognized streptococcal puerperal infection frequently owes the ease with which it gains access to the maternal tissues to the damage done thereto by an initial, hitherto unrecognized, and possibly transient anaerobic infection.

From the cases cited above, the following classification is suggested for infections of women during the puerperium by the pathogenic anaerobic bacteria. It must be remembered that in any individual case, classification can only be arrived at after the event, and it is impossible to predict into which group the patient will eventually fall. Some attempt at prognosis can only be made by a consideration of the gravity of

the various predisposing conditions, which have already been enumerated, and every case must be regarded as potentially severe.

(1) *Saprophytic Infection.*—Seen in those cases in which bougies had been introduced into a uterus containing a dead fœtus, and the subsequent labour was normal. There was no evidence of puerperal infection, the organism disappearing from the lochial discharges in a few days. These were the only cases in which *B. aerogenes capsulatus* appeared to play the part of a saprophyte.

(2) *Local Uterine Infection.*—Seen in those cases in which intra-uterine manipulations had been performed after the death of the fœtus and in which actual delivery was delayed.

(3) *Generalized Infection.*—This is a condition characterized by severe toxæmia and is almost invariably fatal. That form in which multiple gas abscesses appear throughout the body, before or after death has occurred, has been recognized as a rare complication of the puerperium for many years, and is probably the least common form of fatal anaerobic infection. It appears to follow a definite set of circumstances, already described.

Death, in cases resulting from an intensive toxæmia, may supervene with extreme rapidity. As illustrated by the single case mentioned in the series, it seems that this type of infection would occur in a patient whose resistance is greatly weakened by such circumstances as loss of blood, lack of sleep, or a severe toxæmia of pregnancy. This type of infection is not only not recognized in this country, but may even be ridiculed when suggested. Lehmann, in his investigations on many hundreds of cases of *B. aerogenes capsulatus* infection following abortion, found and recognized the condition again and again. It is held that this form of infection may be responsible for a large number of those cases classed in any report on maternal mortality as cases "of sudden death" or death as the result of "shock." Further investigation may show, for instance, that many cases of eclampsia in which death followed instrumental interference with pregnancy will fall into line with the fatal case described in this series. These suggestions can only be confirmed or negatived as a result of a fuller investigation of those cases of maternal death whose nature has hitherto remained somewhat obscure.

Although the cases described in this series appear to fall into defined categories, it is emphasized that this may have resulted from varying virulence of the organisms introduced. It would therefore be in order that the worst form of "gas infection" should follow only trifling manipulations, provided that the other stipulations were fulfilled.

Time will not permit of a description of the morbid anatomy or symptomatology of this type of infection. The more important aspects of both will be included in a full consideration on the diagnosis of the condition.

The first point to make clear is that, in order that treatment may be begun at a time when it is likely to be effective, the nature of infection must be diagnosed, or at least strongly suspected, before the onset of the symptoms or physical signs. These signs and symptoms, in the first place, fall into line with those of any bacterial infection or toxæmia, and, in the second place, are either of such severity that death occurs before there is any time to give adequate treatment, or, and perhaps more often, are hopelessly masked by a superadded pyogenic infection.

From these remarks it may be surmised that the diagnosis is not made from the symptoms or signs produced by the condition, and this is the reason why these are not discussed at all in this paper.

The onset of an infection of this nature may be anticipated by preceding events. Thus, anaerobic infection of the fœtus and placenta is almost certain to occur following any intra-uterine manipulation that takes place when the child is dead *in utero* and remains undelivered for some hours following this introduction of infection. The likelihood of maternal infection may be surmised with considerable

accuracy when consideration is made as to the probable damage to maternal tissues with concomitant lowering of local resistance. At the same time allowance must be made for the general resistance of the woman to infection—which of course is influenced by such events as exhaustion, loss of blood, or any debilitating disease—and for the varying virulence of the infecting organisms.

In all such cases the fœtus and placenta should be examined for the presence of the pathogenic anaerobic bacteria. In addition, the lochia should be examined every twelve hours until the absence of an anaerobic infection can be declared with some certainty, and this is possible about forty-eight hours after delivery.

The German workers all emphasize the importance of finding the organisms present in the blood-stream. Septicæmia during the puerperium only appears to occur in the more severe cases, and then often, perhaps, as a terminal event, although Lehmann believes that a transient bacteriæmia is usually to be found following curettage of a really septic uterus. Therefore the bacteriological examination of the lochia is a more certain aid to diagnosis than that of the blood or urine, though both these investigations may be performed when the first gives a positive result. Certain stipulations are made before a bacteriological investigation of the lochia is to be of any value. The actual identification of the pathogenic anaerobic bacteria—of which the *B. aerogenes capsulatus* is probably the most important—is not always easy, and requires cultural reactions and animal inoculations before the true nature of the organism is established. Further, the presence of these organisms, as illustrated by certain cases mentioned before, does not necessarily mean serious infection. True infection is associated with proliferation and, in consequence, the first essential is that the relative abundance of the bacteria in the lochial discharges should be ascertained. This is done by spreading a standard loopful of the material to be examined over one square inch of a glass slide.

It is recommended that whenever the possibility of an anaerobic infection is suspected, a film of the lochia, or of the placental or fœtal tissue, should be examined by Gram's method of staining. The diagnosis is not difficult, should the *B. aerogenes capsulatus* be present in large numbers. The difficulty arises when only a few of the organisms are to be seen in each microscopical field; in that case, however, the infection is probably a mild one, and the presence of the organisms is consequently of less importance. The early diagnosis of the nature of the infection by this method is of the greatest value, as will be seen when the treatment is discussed. The final isolation of the organisms may then be left in the hands of the expert bacteriologist, and is of little importance.

The presence of the vaginal bacillus, or rather one form of this organism, may cause difficulty. The differences between the two organisms will be stated in full elsewhere. Suffice it to say that no difficulty will be experienced by anyone familiar with the examination of smear preparations of lochia and with the appearance of the *B. aerogenes capsulatus*. The vaginal bacillus is present usually in long chains, possesses no capsule, and stains evenly. On superficial examination, however, the microscopical appearances of the two organisms are alike, and on culture the confusion may be increased by the fact that the vaginal bacillus grows readily under anaerobic conditions, in many instances with the production of gas.

Treatment.—Prophylaxis: It has been found, both from the cases reported in the literature and from those investigated in this series, that infection of a serious nature in the puerperal uterus almost invariably follows gross manipulations or any manipulations performed some time before delivery, when the child is dead. The cure for the first evil—gross manipulations—is obvious, and lies in better midwifery. The second cause has some bearing on the present teaching of midwifery. Some instances may be considered:—(*a*) An obstructed labour is due to persistent occipito posterior position; the head is held up in the cavity of the pelvis, and the fœtal heart sounds have not been heard for some time. Internal rotation at this stage would be difficult

and, inview of recent findings, dangerous. The simple application of forceps is strongly indicated. (*b*) Labour is obstructed by a breech presentation with extended legs. Evidence goes to show that the child has been dead for some hours. It is advised that under no circumstances should an attempt be made to bring down a leg, but that the child should be extracted as gently as possible with the blunt hook.

In both these instances, whatever steps were taken to aid delivery, gas infection would probably not occur, or if it did occur, would not be dangerous to the mother, provided that delivery was reasonably rapid and carried out with the minimum of maternal injury.

Similarly the use of Willett's forceps in cases of placenta prævia is advocated most strongly in preference to the usually violent intra-uterine manipulations necessary when plugging the lower uterine segment with the half breech or de Ribes bag. In short, whenever the child is dead, let its delivery be in the gentlest and most rapid manner possible.

The Use of Antitoxic Serum.—In contradistinction to the streptococcal infections, powerful antitoxic sera can now be obtained for the *B. aerogenes capsulatus*. Prophylaxis: The administration of the appropriate antitoxin has been advocated in order to prevent infection. To suggest that a prophylactic injection should be given to every woman after childbirth is obviously absurd. Puerperal infections with the anaerobic bacteria are relatively rare. Further, it has already been demonstrated that this type of infection usually followed a certain definite combination of circumstances. In these cases, therefore, the administration of a prophylactic dose of antoxin is strongly advocated. The prophylactic use of antitoxin is limited to selected cases. Injection of antitoxin will not repair tissues that have already been damaged, and it is of the utmost importance that its administration should take place at the earliest possible moment. In other words, it is worse than useless to wait for the tedious investigations necessary for the isolation and identification of the infecting bacteria. Moreover, by the time that the symptoms and signs of the infection are apparent —which is the usual period at which the bacteriology of the lochia, and perhaps of the blood and of the urine, is investigated—the infection is well established and the damage, both local and general, has been done.

It cannot be too strongly urged that in those cases whose nature has already been outlined, and in which anaerobic infection is most likely to occur, a prophylactic dose of antitoxin serum should be administered at the time of—or directly after—delivery, as no estimation can be made as to the rapidity with which an infection of this type can become established or will proceed. In two cases of the series described, the death occurred within a few hours of the introduction of infection.

Antitoxin treatment has been advocated to aid in the abolition of toxæmia, and the reaction is purely quantitative. Toxæmia, however, will of course recur until the removal of the source of the infection. The question of this being effected by surgical means will be discussed later. Again, it is obvious that treatment of a case with the antitoxin for *B. aerogenes capsulatus* is useless when the original anaerobic infection is superseded by a pyogenic infection, such as commonly occurs if the patient survives for any length of time.

The use of antitoxin to prevent the spread of an anaerobic infection, or to overcome it, has been suggested. This can only be made effective by maintaining a high local concentration of antitoxin, either by local injection, or by administration of massive amounts into the circulation. Weinberg, amongst others, has observed a greatly increased leucocytic reaction around the infeeted area following local injection of antitoxin, but its application in the case of infection of the puerperal uterus is impracticable.

Dosage.—To be effective, the antitoxin must be administered before the tissues are permanently injured by the toxin. Further, the amount and strength of the

toxin cannot be gauged until the clinical manifestations appear and the damage has already been done. In other words, the toxin must not be allowed to gain the upper hand. Therefore in all those cases in which the nature of the infection is strongly suspected for any reason, the earliest possible administration of a reasonable dose of antitoxic serum is advocated. A prophylactic dose must be as large as the initial therapeutic dose, i.e., 40 c.c. of the concentrated serum. Amongst the cases treated in this series, as many as ten doses of the equivalent of 20 c.c. of concentrated serum, preceded by an initial administration of 40 c.c. of concentrated serum, have been given. Shoula the patient be seen for the first time when the infection is established, part or the whole of the initial dose should be given intravenously. Subsequent dosage depends entirely on the progress of the case, as shown by any alteration in the symptoms, or by the changes in appearance of the direct smear preparations of the lochia, which are made every twelve or twenty-four hours, as regards increase or decrease in the numbers of the anaerobic bacteria. In the cases investigated in this series, a mixed anaerobic infection has always been associated with, or immediately followed by, a superadded pyogenic infection, in which event the use of the polyvalent serums would be of little use.

Surgical Interference.—The principles of the surgical treatment of gas infection of war injuries consisted in the free excision of dead or damaged tissues, before or when infection was established, and free incision and drainage when ablation was impossible. It will now be considered whether these principles can be applied to puerperal infection with the pathogenic anaerobic bacteria.

Many of the German workers recommend hysterectomy in cases in which gas infection of the uterus is established. In one case of the series of cases investigated, that operation was performed. Although the patient made an excellent recovery from the operation, the treatment was not justified, because the infection involved not only the uterus but also the upper part of the vagina and the pelvic cellular tissue. Furthermore, there is much to be said for the view that if the patient's condition is bad enough to warrant hysterectomy, in all probability the damage to the heart, muscle, liver, kidneys and other organs of the body has already been done, and perhaps the organisms are even in the blood. If hysterectomy is to have a place in the treatment of infections of this nature, it must be performed at an early stage, be accompanied by administration of intensive doses of antitoxin, and be limited to cases in which every effort to find evidence of extra-uterine infection has failed. Seeing that the diagnosis of the exact extent of the infection is extremely difficult, and that if the toxæmia is present the damage has been done, it is doubtful whether this operation can be advised under any circumstances. Among other contra-indications would undoubtedly be the risk of unnecessary performance and also, in the event of recovery, the resulting disability. Surgical aid in the performance of hysterectomy in cases of anaerobic infection of the puerperal uterus is not therefore recommended.

In conclusion, stress is laid on the great danger of leaving a dead fœtus undelivered, or of performing any but the most gentle intra-uterine manipulations in the delivery of a child that has been dead *in utero* for some hours.

Mrs. IVENS-KNOWLES said that the subject of anaerobes was one in which she was specially interested, as during the late war she had had the opportunity of treating many cases of gas gangrene,[1] and that experience had demonstrated the great value of serum therapy.

1 See "A clinical study of anaerobic wound infection, with an analysis of 107 cases of gas gangrene," by Frances Ivens, M.S., *Proc. Roy. Soc. Med.*, 1916, x (Sect. Surg., 29).

She had recently reported a severely infected puerperal case in which Weinberg's anti-anaerobic and anti-coli serum had been successfully employed, and in which the *B. aerogenes capsulatus* had been demonstrated by animal inoculation. She agreed with Mr. Wrigley that muscular trauma was an important factor, as these organisms seemed to have a special affinity for injured muscular tissues. She advised the prophylactic use of serum in cases of prolonged labour, in which fæcal contamination was probable, and especially when the fœtus was dead.

Section of Otology.

(Special Summer Meeting at the Nottingham General Hospital, June 27 and 28, 1930, continued.)

Repair in the Middle Ear.

By A. Lowndes Yates, M.D.

Repair is the process by which the function of an organ is returned to normal. Any account of the process of repair of the middle ear must include a description of the normal condition, of the pathological conditions encountered, and of the changes which occur in the process of healing.

Some five years ago I became interested in the repair of nasal and of aural epithelia and found that in certain cases, although repair of the epithelium apparently took place, the hearing did not become normal. It was therefore necessary to conduct experiments to discover, if possible, the relation between the healing process and the restoration of the function of the middle ear.

The investigation was divided into two parts, one dealing with the functions of the middle ear and the methods by which these could be restored, and the other dealing with restoration of the function of the epithelium and the nature of the normal function of this tissue.

Part I.—(A) Investigation of the Functions of the Middle Ear.

A large working model of the middle ear was constructed and in the place of the cochlea a microphone was fitted; this connected with a loud speaker. The tensor tympani was represented in the model by an elastic band which could be so adjusted that it drew the malleus into contact with the incus, or, alternatively, was relaxed so that the cog processes of these two bones were separated. When they were thus separated a sound falling on the artificial tympanic membrane caused no sounds to emanate from the loud speaker.

As the tensor was shortened, the middle tones, those about 512 d.v., were heard, and the tones above and below this in pitch were heard progressively less well. As the band was further tightened, a point was reached at which all the tones came through with equal power and on further tightening of the band the lower tones were lost, and the highest tones in the region of 4,000 were heard from the loud speaker with their normal intensity. These notes were produced by an audiometer.

It therefore appeared that in the artificial middle ear there were three primary positions of the ossicles: (1) a position of rest, in which only loud sounds, or sounds which had special penetrating power, were audible; (2) a position of listening, in which the ossicles lay in a position in which maximal hearing of all the notes

of varying pitch took place, and (3) a position in which the membrane was indrawn in a manner similar to that which evidently took place at the summit of a positive wave of sound when it fell upon the membrane. This last position may be described as that of " having heard."

It was clear that, if this experiment actually represented the condition in the middle ear, deafness might result either from the maintenance of the position of rest, or from the maintenance of the position of " having heard."

Various experiments were performed in which the ossicles were either fixed together or to structures in their neighbourhood, but the results in the artificial model were so complex that it was impossible to say that they represented any definite type of deafness. Finally, in further attempts at such experiments the model was unfortunately destroyed and has not been rebuilt. I showed a similar model, designed for use as a gramophone record, to this Section in 1927.

Part I.—(B) The Methods by which the Functions of the Middle Ear can be restored.

If the membrane is indrawn it is the custom to inflate the ear. In the portion of the paper which deals with the restoration of the function of the epithelium, evidence is brought forward which suggests that to inflate the ear is not good practice in a large majority of cases, for the infective products which block the tube and cause the vacuum otitis may thus be blown into the cavity of the middle ear and there set up inflammation.

As a result of data gathered in this investigation, it would appear that a better practice is to aspirate the mucus from the interior of the Eustachian tube by means of the catheter originally designed by Weber and Liel.

During the course of this investigation the effect of the cerumen of the ear received consideration, and the late Professor Starling was good enough to give me his advice upon this matter. It appears that cerumen is secreted in a very fluid form and runs over the tympanic membrane, thus oiling it and preventing the evaporation which possibly occurs from the mucus which is present in the middle ear. This view is based upon the following experimental evidence :—

A microscopic slide, having a well for the examination of the hanging drop, was used and the wells in two such slides were filled with mucus. Over the top of them a piece of paper was attached by gum. In one of these preparations the paper was treated with an artificial wax, and in both a cover formed of wax was placed upon the slide. This cover was an inch thick and was perforated by a hole which represented the external auditory meatus.

Both slides were re-examined at the expiration of three days and the paper was removed. It was found that the mucus in the specimen in which the paper was not oiled had formed adhesions between the paper and the inner surface of the glass, but had formed no such adhesions in the specimen in which the paper had been oiled. Professor Starling was the first to suggest that the function of the cerumen was to prevent evaporation of the mucus, and this experiment seems to confirm his view.

Further confirmation of this view is obtained by a consideration of patients who are suffering from an obstruction of the Eustachian tube and impacted wax. In these, on removal of the wax, the membrane is almost always caused to return from its indrawn position by inflation of the middle ear, which observation is in striking contrast to the fact that when wax is absent from the meatus, it is generally a matter of considerable difficulty to break down the adhesions in the middle ear by inflation.

I therefore filled the ears of certain patients with an artificial wax and tried the effect of inflation when the wax had been removed. In cases in which the history of deafness was short and in which the adhesions had resisted attempts at inflation, it was found that, after the ear had been filled with wax for periods varying between

7 and 28 days, the adhesions could be broken down in about 25% of cases. Some of the remainder yielded to inflation after a further period of treatment with the wax.

In cases in which the history of deafness was a long one, the results were naturally less successful, but one or two successes were recorded, and in many cases a considerable improvement in the hearing was effected. On following up the subsequent history of the cases, however, it was found that this improvement was not maintained.

This and the other evidence on this question suggests that evaporation can occur through the tympanic membrane, and, in the milder and more chronic states of inflammation, may hinder the process of repair.

In certain states of deafness there is some not very conclusive evidence that the membrane lies in a position of rest and cannot be brought into the position of listening. In the condition known as subacute otitis media, the membrane is occasionally bulged out by mucus lying between it and the inner tympanic wall. This mucus is removed at intervals, apparently by ciliary action. The symptoms are pain and, later, partial deafness, which increases, and it is in these cases that we find alterations in the hearing similar to those by which we diagnose the presence of "otosclerosis."

In certain of these cases the patient may hear better in the morning than in the evening and, at times, for a brief period in the day, he may suddenly, without apparent cause, hear normally for a few moments and then his hearing power departs as suddenly as it was restored.

There are two possible explanations of this phenomenon, namely: (1) that the tensor tympani is stretched by the chronic out-placed position of the membrane, due to the mucus which has collected in the middle ear, and (2) that this stretching is followed, as in other muscles, by a loss of tone and failure of voluntary contraction. But, as in other muscles so affected, a sudden need may temporarily allow such a degree of contraction as permits the muscle to perform its function for the moment, after which it passes once again into its former state of loss of tone, being moreover more fatigued as a result of its temporary forced contraction.

Another view by which this might be explained, is that a drop of mucus finds its way to a position which causes separation of the cog processes of the malleus and the incus. Whichever view we take, it would seem that there is evidence that the condition is one of inability to listen rather than one of inability to hear.

If a pledget of cotton wool soaked in liquid paraffin is placed in firm contact with the tympanic membrane, hearing, if the membrane is out-placed, will be, in many cases, temporarily restored, and the restoration of the hearing may possibly be rendered permanent if the tympanic membrane is in-placed for several weeks, or months, by pressure of artificial wax. It is necessary to remove the artificial wax at intervals, for, like the ordinary cerumen, some portion of the wax is absorbed by the skin and it becomes harder and more difficult to extract.

If we accept the view that listening is, in part, the result of the contraction of the tensor tympani which brings the cog processes of the malleus and incus into contact, this and the other evidence on this question points to the fact that repair within the middle ear may take place fully but leave the structures of the middle ear in a position in which the act of listening is carried on with difficulty.

In this investigation it was further found that certain cases showed a high degree of auditory fatigue. In many of these cases there was evidence of a lesion of the perceptive mechanism. In a few, no lesion of the perceptive mechanism could be discovered and on testing these with very special care, it was found that they had no power of resting their ears. For some reason the mechanism of the middle ear was retained in the "position of listening." These cases are comparatively frequent but it requires very careful testing to demonstrate their presence.

One feature which is common to these patients is their difficulty of hearing in a

noise, in striking contrast to the condition obtaining in patients with an out-placed membrane, in whom there is generally some degree of paracusis.

PART II.—(A) INVESTIGATION OF THE NORMAL FUNCTION OF EPITHELIUM OF THE MIDDLE EAR.

The mucous membrane of the middle ear contains glands which secrete mucus, increasing in amount as it passes from the aditus to the pharyngeal opening of the Eustachian tube. This mucus is carried to the nasopharynx by the action of the cilia which are sparse within the middle ear and increase in number and activity as we trace the cavity of the middle ear and the Eustachian tube to its opening in the naso-pharynx.

The following experimental evidence is offered for consideration :—

If, in an ear in which there is a perforation of the tympanic membrane, but in which discharge has ceased, flavine is poured into the meatus and then indigo-carmine is introduced into one or more of the nasal sinuses, the flavine is conveyed down the Eustachian tube and to its opening in the concavity of the cushion. The blue dye from the sinuses is conveyed around the convexity of the cushion in a manner which has already been described elsewhere. The two streams do not mix until they have passed for some considerable distance, and it is plain that there is here a method of protection of the Eustachian tube against infection.

When I followed up this observation on cases in which sinusitis was present with a chronic state of inflammation of the middle ear, I found that these fell into two separate groups. In one group the pus flowing over the convex surface of the cushion had caused a swelling of its mucous membrane and an obstruction to the opening of the tube which had increased the liability to infection. In the other group, the sinuses and middle ear appeared to have both been infected during an attack of "influenza."

I therefore examined the condition of the cilia in attacks of "influenza," using the coloured dyes to indicate the speed of action of the cilia, and I found that within a few hours of the onset of the acute and dry rhinitis, the cilia were paralysed through the nose and naso-pharynx. I was unable to demonstrate this palsy in the Eustachian tube, but there can be little doubt that the mucous membrane in this situation shares in the universal inflammation.

The cilia in the nose begin to work again at a period which varies between three and ten days after "influenza" and the longer that their palsy lasts, the greater seems to be the liability to sequelæ in the middle ear.

During an attack of "influenza" no secretion can be aspirated from the nose unless a sinusitis has been present previous to the illness. After an attack of "influenza" a reaction of the mucous membrane takes place, and the nasal discharge may be free or absent.

In cases in which discharge is free, leucocytes and epithelial cells are present in the mucus, but when discharge is scanty it contains many epithelial cells, and there seems to be evidence that cells damaged by the inflammation are cast off and regenerated.

That the ciliated epithelium can be regenerated is, I am aware, a view which is not generally held, but the evidence of desquamation, not only in this type which I am now considering, but also in other cases of inflammation, and the reappearance of ciliary function after profound and frequently prolonged desquamation, seems to prove the matter. Moreover, if an area of epithelium is surgically removed from the nose, the ciliary stream is only temporarily absent and returns in about six weeks. Hence I believe that the ciliary function can be regenerated, and if this view is correct, that it has some importance in that the regeneration of the ciliary function in the ear is the vital step towards repair.

If the ciliary function does not return in the Eustachian tube, and if the mucous glands continue to secrete, there is no mechanism by which this mucus is removed, and the Eustachian tube contains a mucocele as a result of which the middle ear is always in a state of mild chronic inflammation and suffers from one of two types of deafness; either from a vacuum otitis, or from the type of deafness which I associate with an out-placed membrane, that is to say, with a membrane which cannot be indrawn to the position necessary for the act of listening.

Experiments on Mucus.—It has not been possible to carry out a full investigation of the solvent action of the mucus on the cells and micro-organisms which are frequently to be found within it. The following experiments suggest that treatment may, with advantage, be modified by means of information gained by an estimation of the solvent action of the mucus on the cells and micro-organisms.

Clinical Investigation: (A) Cases in which improvement was apparently spontaneous.—Mucus was aspirated from the Eustachian tubes and placed for examination between a sterile slide and cover slip. *Group* 1.—In this, the cells consisted of leucocytes with micro-organisms which were intracellular. When allowed to stand for about twelve hours, the leucocytes dissolved as did the micro-organisms, clear mucus being left. *Group* 2.—In this the cells were leucocytes and the micro-organisms were partly intracellular and partly free within the mucus. On standing for twelve hours, the leucocytes dissolved leaving the micro-organisms undissolved in many cases. *Group* 3.—In this, the cells were epithelial. After standing for twelve hours the cells were dissolved in certain cases and undissolved in others. Intracellular micro-organisms were often present and these were not dissolved.

If in any of the above groups the mucus was diluted, the solvent action was diminished, and in certain specimens dilution with saline seemed to convert the anti-bacterial mucus into a medium in which the micro-organisms could be cultivated with considerable ease.

The types of micro-organisms which produce diapedesis of the leucocytes, or shedding of the epithelium, belong respectively to those two main groups: (1) in which the defence of the body is by leucocytes, and (2) in which the defence of the body is by anti-bacterial substances elaborated in the serum and permitted to escape into the mucus.

In many cases the thickness of the epithelial cells suggested that they were derived from deeper layers of epithelium and that the process of desquamation and regeneration had reached a balance as a result of which repair could not take place.

(*B*) *Cases which did not show spontaneous improvement.*—(1) Acute conditions: (*a*) The leucocytic group. The leucocytes were very numerous and their solution did not take place in 12 hours. Free micro-organisms were present in the fluid which formed an efficient culture medium. (*b*) The serous group. In this the Eustachian tube and middle ear shared in an acute desquamative process which affected all the nasal mucous membrane. The nasal mucous membrane had recovered first, leaving a focus of infection in the ear, which focus was too small in area to permit of a sufficient quantity of toxins to reach the blood-stream and thus to generate enough anti-bacterial substance to kill the micro-organisms. (2) Chronic conditions: (*a*) The leucocytic group. In this the leucocytes dissolved but the micro-organisms which were extra-cellular did not dissolve. (*b*) The serous group. In this there was a higher stage of that process of a balance between desquamation and regeneration which has been described above. (The author has been referred to the work of Flemming on this matter).

It is probable that the very small amount of cultural work which has been carried out does not permit of any statement being made with regard to the cultural characteristics of the various types of mucus. One fact is noted, however, as worthy of record. It has seemed that if mucus is allowed to dry rapidly, it loses its anti-

bacterial efficiency and, when re-dissolved, can become an efficient culture medium for the micro-organisms contained within it. It is possible that this fact may explain the acute inflammatory processes in the ear which follow nasal douching or sea-bathing. It has been noted that during the recovery stages of a cold, particularly in the summer when the air is dry, the mucus in the nasal airway and in the naso-pharynx tends to dry, and thus may reproduce within the nasopharynx and the ear the conditions which are here described.

It would seem therefore, that the decision as to whether to syringe an ear during the course of inflammation requires nice judgment, for in certain acute states in which the mucus has lost its bactericidal action, syringing may do good. In states in which the destructive power of the mucus is high, syringing will diminish it. There is, of course, no difficulty in reaching a decision on this point if the mucus is examined and its bactericidal properties are assessed.

Repair within the middle ear seems therefore to depend upon the interplay of two mechanisms; (1) that which is concerned with the removal of the mucus by the ciliated epithelium and, (2) that which is concerned with the destruction of the agents which produce infection.

From the above experiments it seems probable that repair within the middle ear depends in part, at any rate, upon the efficiency of the bactericidal properties of mucus, and in part on the establishment of a condition of immunity in the serum against the infecting micro-organisms.

It has been noticed that when the mucus contains leucocytes and some such micro-organism as the *Staphylococcus aureus*, desquamation was not great and that the ciliated epithelium began to act again quite quickly after the resolution of the inflammation.

In cases in which the cells which were visible in the mucus represented desquamated epithelium, the rate of repair was considerably slower. On the other hand, in the desquamative type there appears to be little, if any, tendency to the formation of fibrous tissue in which this type differs from that in which the leucocytes are present.

During repair, the position of the component structures of the middle-ear, relative to each other, is of more importance than the actual act of hearing.

Part II.—(B) Investigation of the Methods by which the Process of Repair can be assisted.

The recognition of retention of products of inflammation in the middle ear is essential, before successful treatment can be undertaken.

In acute states the spread of inflammation from the lower compartment to the upper compartment of the middle-ear may be prevented by the folds of mucous membrane which connect the ossicles to the anterior and posterior walls of the cavity. It appears that if these can be recognized as swollen structures there is pus above them in practically every case. This pus will be prevented from escaping by their presence and a myringotomy must penetrate these swollen folds so as to drain the part above them.

If in a few days' time the quantitative estimation of the hearing of the upper and lower tones is not improving, the question of the performance of mastoid drainage will have to be considered, particularly in adults, for if the pus is not escaping from a mastoid which is infected, the hearing power will in the course of weeks be damaged so severely that, even if it is regained, it is probable that the subsequent contraction of the fibrous tissue in the folds will lead to high degrees of deafness in such a large majority of cases that the performance of a mastoid operation will be justified.

It seems to be a fact that the proteolytic ferments which are elaborated by the micro-organisms are the most important element in the prevention of repair in the

leucocytic type of inflammation. It is, in fact, these ferments which have caused the perforation of the membrane and when a perforation has resulted it is certain that the digestive power of the pus has similarly, though less obviously, caused destruction in other situations in the middle ear.

Experiment tends to prove that the proteolytic ferments of the micro-organisms behave like the intestinal ferments, that is to say, the reaction of the medium in which these ferments act must be of an acidity, or an alkalinity, suitable to the ferment.

Some micro-organisms cause acidity in the pus that they produce and some cause alkalinity. If the reaction of the pus to litmus is obtained, the following line of treatment may be carried out with good results. If the pus in a case of chronic suppurative otitis be acid, the ear is douched with alkalies and as soon as the discharges become alkaline the intensity of the inflammatory process begins to be reduced. If the pus is alkaline, boric acid may be similarly used with good results. The above has been christened "amphoteric treatment."

Whenever an ear in a state of acute inflammation is douched there is a danger of interfering with the anti-bacterial power of the leucocytes and, for this reason, the amphoteric treatment is only used in cases in which the acute stages of inflammation have passed off and in spite of careful treatment the discharge is not diminishing and the size of the perforation is increasing.

The few experiments that I have been able to conduct are not sufficient to place the amphoteric treatment, and the principles on which this depends, on a basis which permits of a more dogmatic statement than that the method is worthy of investigation.

The recognition of the desquamative states in contra-distinction to those in which the leucocytes are active, is of importance in considering the means of treatment. In the leucocytic states of inflammation the micro-organism is destroyed by leucocytes and is, as a rule, not of the type which yields antibodies in the blood.

The desquamative states seem to be caused by those types of micro-organisms which produce a state of immunity to themselves in the blood and, if the aural inflammation is but a part of a general inflammation of the mucosa of the nose, immunity will be established; there is some reason to believe that the serum which escapes from the denuded mucous membrane is the agent which destroys the micro-organisms.

In certain states, however, the mucous membrane of the ear seems to be the only area thus inflamed. Such an area is not sufficient to produce immunity and the inflammatory process thus continues. It is in these states that we find that type of inflammation in the ear which can be recognized by a grey, out-placed, transparent membrane, and if Siegle's speculum is introduced, the alternate compression and rarefaction of the air may reveal small bubbles which move under compression and rarefaction into the pouches and folds of mucous membrane in a manner which is very interesting.

On testing the hearing in a type of case like this, particularly in a chronic case, one is immediately struck by the similarity between the type of hearing found in these chronic cases and in the condition known as otosclerosis.

In some of these cases the inner tympanic wall is very red, and the tympanic membrane is transparent; they resemble closely the condition which has been described under the name of otosclerosis and, in fact, it is believed by some that otosclerosis in its clinical form is a manifestation of the terminal results of this inflammatory process. Now otosclerosis is a condition of the labyrinthine capsule and, therefore, is a state which cannot be recognized until the patient has died and his ear has been submitted to microscopical examination.

It would help otology enormously if it was agreed to drop the term "otosclerosis," and if research centred round these desquamative types of inflam-

mation which produce symptoms indistinguishable from those stated to be present as a result of the lesions of the labyrinthine capsule.

The line of treatment that I have adopted in these cases has been successful only in the early stages, and this line of treatment is repeated aspiration of the Eustachian tube, combined with myringotomy if necessary.

The Need of Recognition of the Position of the Ossicles during the States of Repair.—It appears that if the membrane is bulged out for long periods in the minor states of inflammation, a type of deafness results which has been described as that of inability to listen. Should this condition manifest itself during the active stage of inflammation, a myringotomy will relieve the tension, and the need for this myringotomy has to be diagnosed almost entirely by the tests of hearing. These have been already described to the Section.[1]

Broadly speaking, the graph shows no alteration in the power of hearing the middle notes in the region of 512 d.v., and an inability to hear the highest and lowest tones even when of considerable intensity. If, in addition, the tests of hearing show a progressive loss of bone conduction, this will in itself suggest the need for myringotomy during the persistence of the inflammatory process.

If the membrane has been pushed into contact with the inner tympanic wall by impacted wax, adhesions of serum or mucus may form within the middle ear. These are always soft and can be easily broken down, but if they are not broken down and the wax is not renewed, they tend to permanence and this fact suggests the importance of supplying artificial wax, or possibly some oil, to the tympanic membrane during the act of repair; certainly I have found that the results of treatment are considerably better.

In every state of inflammation of the middle-ear repair may be prevented by conditions which affect the general health. If repair is sluggish and if the process of inflammation is not diminished by our treatment, it is desirable to make a general examination of the body and, if it be advisable, to give aperients, particularly calomel. I have often noted the improvement which is obtained, particularly in the desquamative states, when calomel is administered in small doses for a few days.

The desquamative states are particularly prone to be associated with anæmia, and should this be the case the administration of liver is desirable, and may be combined with that of iron.

If acidosis is present it is desirable to combat it with alkalies which should be given in sufficient doses to make the urine alkaline.

Conclusions.

As a result of observations made during this investigation, I venture to offer the following conclusions. (1) Repair within the middle ear, when it succeeds, does so by reason of the activity of the bactericidal action of the mucus and of the cilia which move this mucus on. In practice it is found that the state of repair of the middle ear can, to some extent, be assessed by the discharges which lie within the tube, or escape through the perforation in the tympanic membrane.

It seems to be of some importance to recognize the two main types of inflammation in the ear, the leucocytic and the serous, and to endeavour to treat each type in an appropriate way.

The cilia are the only means by which the mucus is removed from the middle ear and if these cease to act, as a result either of palsy or of desquamation, a chronic inflammation is induced within the middle ear.

(2) It would appear that the majority of lesions which produce deafness arise as a result of inflammation in the middle ear, and that there are two primary positions

[1] *Proceedings*, 1928, xxi, 868 (Sect. Otol., 34).

in which the normal ear hears with a much diminished acuity. These two positions are the position of "having heard" and the position of "rest."

It is suggested that two common forms of deafness are due to the auditory mechanism becoming fixed in these positions while, in addition to these, fixation may occur in the position of listening which makes it impossible to rest the ear.

Discussion.—Mr. ALEXANDER TWEEDIE said he did not know whether the model referred to was intended to show the part which was played by the tympanic membrane in the function of hearing. He (the speaker) suggested that in the investigation should be included an experiment which would differentiate between the tympanic membrane factor in the transmission of sound, if any, and the value of the integrity of the two windows. He, and others also, had seen cases in which the tympanic membrane was lost and yet the hearing was almost as good as normal.

Mr. WATKYN-THOMAS said that, in connection with Mr. Lowndes Yates's views, it was interesting to recall that the late Mr. Arthur Cheatle had pointed out how rarely cerumen was ever seen in the ears of patients suffering from clinical otosclerosis.

In the treatment of Eustachian catarrh, he (the speaker) had practised aspiration as advised by Mr. Lowndes Yates, instead of inflation, during the last six months, and was satisfied with the results.

He had recently had a case which demonstrated beautifully the "out-placed" position of the ossicles. A hospital patient with chronic discharge from the ear had a degree of deafness which appeared to be excessive for the amount of tympanic destruction. A conservative operation was performed. The changes in the antrum were slight, but when the attic was opened it was found that the bands were so much swollen that the malleus and incus were forced apart.

Mr. L. GRAHAM BROWN said that Mr. Lowndes Yates, in dealing with the physiology of hearing, had stated that the tympanic membrane and auditory ossicles played a great part in the transmission of vibrations to the internal ear, and on that theory had spoken of the mechanism of these ossicles; how the tympanic membrane might be in a state of repose or a state of listening, which depended on the distance between the cog-like processes of the malleus and the incus. Nothing, however, had been said by Mr. Lowndes Yates about the movements of the inner part of the ossicular chain, namely, the incus and stapes and the attachment of the stapes to the oval window. He (the speaker) thought that there would obviously be a different prognosis when disease affected only the tympanum proper and the tympanic portion of the ossicular chain, from that when the neighbourhood of the windows was involved, since in the latter case there must be inflammatory conditions affecting that portion of the chain. Therefore he surmised there would be a means of distinguishing between the inflammatory condition for which the prognosis could not be anything but very poor—probably hopeless—and that in which otosclerosis could well be included, and that type which affected only the malleolar portion of the ossicular chain and which would be more amenable to treatment.

With regard to the question of hearing: otologists were becoming more and more firmly convinced of the truth of the theory that vibrations were not conducted through the ossicular chain, but—and this was quite a different matter—that centripetal sound impulses were conveyed by means of this chain. In other words, centripetal impulses hit on the round window and, by their action on the endolymph, affected the hair-like processes in the cochlear canal.

Mr. W. STEWART said that textbooks emphasized the fact that in chronic catarrh of the middle ear the membrane was indrawn, but he (the speaker) found that it was blown out in 50% of cases. From what Mr. Lowndes Yates had said, he gathered that there were two classes of case: one in which the drum was indrawn, the other in which it was blown out.

Mr. LOWNDES YATES (in reply) said that he did not suggest that inflation of the Eustachian tube ever produced acute otitis media, but he did think that an exacerbation of the chronic otitis media from which the patient suffered could be caused thereby. An immediate good result was obtained by inflation but the infective material was in many cases forced from the Eustachian tube into the middle ear, causing a low-grade inflammation.

The reason why acute otitis media was not produced appeared to be because the ear was already protected against the micro-organisms of the Eustachian tube by the chronic state of inflammation of its mucous membrane.

In reply to Mr. Tweedie, he thought the tympanic membrane did not possess any function of analysis; he regarded it purely as a structure which assisted in differential listening; it was the tympanic membrane which allowed the listener to pick out a particular voice in a conversation in which a number of people were participating. Also, there was some evidence that the mechanism of the middle ear enabled the internal ear to be rested from noises or sounds it did not wish to hear.

Mr. Watkyn-Thomas had recently shown him a case which was a very good example of the out-placed position of the tympanic membrane. He (the speaker) thought that otologists universally recognized the in-placed position of the tympanic membrane as a cause of deafness and believed that this resulted from obstruction of the Eustachian tube. The experimental evidence brought forward seemed to point to the fact that an equally definite type of deafness could be produced when the membrane was out-placed as a result of being held in that position for long periods by mucus lying stagnant in the middle ear.

In answer to Mr. Graham Brown, he had not dealt with the position of the incus and stapes because it had been necessary to limit the scope of the report. He thought, however, that there was no doubt that the incus and the stapes were returned into their normal position, after hearing, by the tension imparted to the round window by the inward movement of these bones acting through the fluid perilymph. After this inward movement these ossicles were returned outwards by a process of recoil and, therefore, at a speed which was dictated, not by the speed of movement of the malleus when it recorded sound, but by the tension of the membrane of the round window. He had investigated some cases in which the region of the round window was filled with granulations and had found that they showed a type of deafness peculiar to that condition.

In reply to Mr. Stewart, he quite agreed that from the point of view of the position of the tympanic membrane, cases of deafness fell into two groups, but he thought that in chronic deafness the out-placed membrane was considerably less common than the in-drawn membrane.

Demonstration of Sound Records.

By A. Lowndes Yates, M.D.

The records consist of sound strips similar to those employed in making talking pictures. They are of value for study, partly because they are records of the movement of the diaphragm of the microphone into which the word is spoken, and partly because there is no doubt that they are actually representations of these movements, for when passed through a talking picture apparatus the word is reproduced from the loud speaker.

On study of these records it is seen that with certain exceptions they record only the vowels, for the consonants are found to be merely methods of starting, stopping or modifying vowel sounds. Exceptions to this rule are the letters S, X and H, which are actually modifications of a vowel so high in pitch that it is composed of a hissing sound.

The interest to otologists appears to lie in the consideration that the normal tympanic membrane conducting apparatus and the fluids of the labyrinth have to make movements similar to those which are recorded. It is also clear from study of the records that if these portions of the hearing mechanism are diseased, certain syllables will be heard less well than others, and those syllables which are known to be lost most early in certain forms of deafness, are seen to be the least defined upon the sound strip. It is not possible, however, from study of a sound strip to state which words will or will not be heard by a person who has a certain alteration in his ear. The auditory intelligence of patients differs vastly, and a high degree of auditory

intelligence will compensate for minor degrees of deafness, whereas a person of low auditory intelligence will be rendered deaf by a relatively slight alteration of his hearing mechanism. The deafness of the latter will be a diminution of the power of appreciation rather than a lessening of the power of hearing simple sounds such as those emanated by tuning-forks, or formed in music.

(The films were provided by the kindness of Mr. F. P. Culbert, of the R.C.A. Photophone Company.)

Some Mechanical Problems in the Making of Cochlear Models.

By GEORGE WILKINSON, F.R.C.S.

THOUGH the resonance theory has always attracted me, as providing a beautiful and complete explanation of the facts of hearing, I wish to state that the cochlear models were not designed for the purpose of proving that, or any other theory. What I set out to do was to embody, so far as possible, the various physical factors which one can recognize as present in the cochlea, and then to see what light the models were capable of throwing on the problem of its action. It has taken some years of experiment to achieve the moderate degree of efficiency to which they have now attained. They are, no doubt, unspeakably coarse contrivances as compared with the marvellously delicate and precise organ which they attempt to imitate. Nevertheless, I claim that the physical principles on which they are constructed are those inherent in the cochlea, and that their action is just what one has always pictured to be the action of the cochlea, on the assumption of the truth of the resonance doctrine.

What are these physical principles? The cochlea is a long, coiled tube divided along the whole length by the spiral lamina, into an upper and lower gallery. The separation of these two galleries is completed by the basilar membrane, which fills in the spiral fissure, and by the spiral ligament, which attaches the basilar membrane to the outer wall of the cochlear tube. We assume that the actual vibrating element in the cochlea is the basilar membrane. This consists of a long row of fine fibres stretched transversely across the basilar fissure, and embedded in a gelatinous matrix of cells, so that it is impervious to fluids. The fibres are graduated in length, the shortest being at the basal end nearest to the oval and round windows, and the longest at the distal or apical end. That the fibres are graduated in tension may be inferred from the structure of the spiral ligament, which diminishes progressively in bulk and density as it is traced upwards towards the apex of the cochlea. The basilar membrane stops short before reaching the extreme apex of the cochlea, leaving a hiatus, the helicotrema, which brings the two galleries into communication. The two openings from the middle ear, the round and oval windows, are placed above and below the commencement of the basilar membrane. The oval window is fitted by a little piston or plunger, the foot-plate of the stapes, to which the sound impulses are transmitted from the tympanic membrane and chain of ossicles. The round window is closed by a simple membrane. The whole is filled with watery fluid.

All these features are reproduced in the models. The basilar membranes are built up of a series of fine wires stretched across the basilar fissure. These are embedded in a double layer of cigarette paper, impregnated with formalized gelatin. The wires are applied to the plate under a graduated tension, which is greatest at the narrow proximal end and diminishes progressively to the broad apical end. Beyond this is a gap representing the helicotrema. The round and oval windows occupy the same

position relative to the basilar membrane as in the cochlea. The "oval window" is fitted with a wooden plunger to represent the stapes. The whole is filled with fluid.

There are, however, limits to the fidelity with which we can copy the mechanism of the cochlea. We have greatly to enlarge the size of all parts of the models, and we are unable to employ materials at all comparable in fineness and delicacy with those found in the cochlea. For the most essential part of the model—the basilar fibres—I have used a phosphor-bronze ribbon only $\frac{1}{80}$th mm. thick. Another feature which I have failed to reproduce is the spiral curve of the cochlea and basilar membrane. I have made attempts to do so in a model [shown], but the

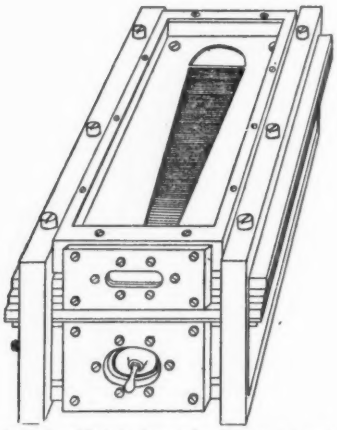


FIG. 1.—Model viewed from in front and above (scale $\frac{1}{4}$.)

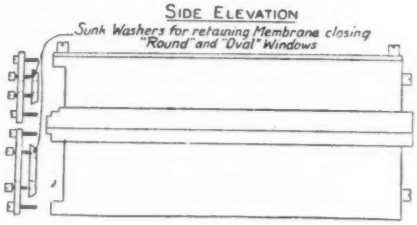


FIG. 2.—(Scale $\frac{1}{2}$).

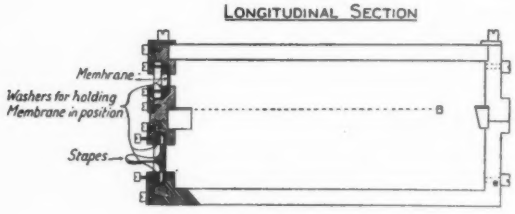


FIG. 3.—(Scale $\frac{1}{2}$).

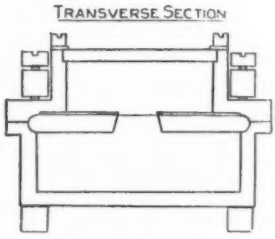


FIG. 4.—(Scale $\frac{1}{2}$).

technical difficulties are so much increased by departing from the rectangular form that it is impossible, for me at least, to obtain any degree of accuracy of graduation, and the result is unsatisfactory.

I believe that all these features—scale, delicacy of material, and spiral form—are of significance in the mechanics of the cochlea, and I realize that my models are far from accurate representations of that beautiful and delicate machine.

The most important practical problem is to obtain accurate graduation of the physical factors regulating the frequency of vibration of the basilar fibres, namely,

length, tension, and mass. Of these factors, tension is, I believe, the most important in the cochlea, as it is in the models. I have had a special winding machine made to ensure an even application of the wire to the plate of the model. The tension is regulated by weights suspended in a loop of the wire over a pulley. These weights are changed for each short length of the winding, so as to give a regular graduation to the tension. It is of the greatest importance that the wire should be applied with an even distance between the turns. The total tension on each transverse sector of the basilar membrane is the sum of the tensions on all the wires comprised in that sector. Thus, if one sector, of say 1 mm. breadth, should include four turns of wire, and another similar sector only two, the tension on the first will be double that on the second sector, and their frequences of vibration will be roughly as 10 : 7, a serious inequality. Unevenness of spacing makes more difference in the graduation of tensions than do small differences in the tension of individual wires.

By use of this winding machine one obtains a fairly satisfactorily graduated series of resonant responses. There are other sources of inaccuracy which are not so easily overcome. These arise from imperfections in the wire itself. In such short fibres very slight inequalities in the wire are capable of producing considerable irregularity of graduation. In one part the wire may be as much as twice the thickness that it is in another. The thicker parts are of greater mass of unit length, and also of greater stiffness. The former consideration is of slight importance, as the mass factor in the graduation depends much more on the fluid load than on the actual mass of the wire itself. The difference of stiffness is of greater importance, as it modifies considerably the form of its vibration. This approximates more closely to that of a thin bar clamped at both ends than to that of flexible strings. It does not vibrate right up to the points of fixation, and a deduction from the actual length of the wire has to be made to arrive at the effective length. The stiffer the wire, the larger the correction to be applied. In such short wires the errors due to variations in stiffness may be considerable. The increased springiness of the thicker wire also tends to increase its rate of vibration. Unless we can employ absolutely even materials these sources of error cannot be entirely eliminated.

I referred to the scale of the cochlea as being probably a significant feature in its mechanics. This is how the matter appears to me. The factors determining the natural periods of vibration of stretched strings are length, tension, and mass, according to the formula—

$$n = \frac{1}{2l}\sqrt{\frac{t}{m}}$$

Though the conditions under which the fibres of the basilar membrane vibrate are not, strictly speaking, those of stretched strings, Helmoltz assumed that the above formula might be taken as, at all events, approximately representing the numerical relations of the magnitude of the various factors. He pointed to the progressive increase in width of the basilar membrane from the base to the apex of the cochlea as evidence of graduation by length. Dr. Albert Gray has pointed out the progressive variation in the bulk and density of the spiral ligament as significant of graduation by tension. I drew attention to the variations in the fluid load on the basilar membrane at different levels as providing graduation of the factor mass. Thus, when the foot plate of the stapes is pushed inwards by a sound impulse, a simultaneous displacement outwards of the membrane filling the round window takes place. There must consequently be a displacement of fluid from the oval window, across the basilar membrane, to the round window. When these impulses are repeated regularly within certain limits of frequency, the displacement crosses the basilar membrane at a particular level, dependent on the frequency, that is to say the pitch, of the note employed. The mass displaced

equals that of a column of fluid whose sectional area is that of the vibrating sector of the basilar membrane, and whose height is the sum of the distances of the sector from the round and oval windows. Each sector of the basilar membrane may be regarded as carrying a load equal to the mass of this double fluid column. The load constitutes the term in the formula for vibrating strings which may be written—

$$n = \frac{1}{2l}\sqrt{\frac{t}{db}}$$

However, it is found by calculation and observation, that this formula cannot be accurately applied to the transverse sectors of the basilar membrane of the models. All these factors—length, tension, and mass—do undoubtedly contribute to determine the levels of resonant response in the basilar membrane, but their numerical relationship is not expressed by the above formula. The reason I believe to be that there is no such mass movement of vibration in the fluid in the models as is implied in the formula, but that eddies and vortices form, which considerably alter the conditions of loading of the sectors. Nevertheless, it seems to me probable that the formula may apply in an organ on the minute scale of the cochlea, as it is

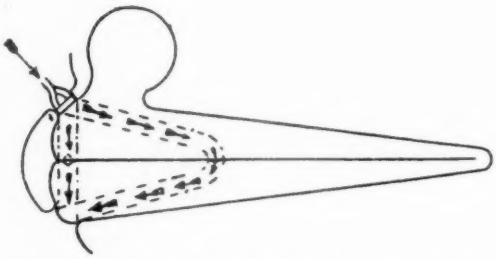


FIG. 5.—Diagram representing the cochlear galleries unrolled, and the fluid columns loading the transverse sectors of the basilar membrane at different levels.

reasonable to suppose that the galleries are too narrow to admit of the formation of eddies. Also, the whole amount of fluid filling the organ is so small that it is possible for it to vibrate in the mass. However, this is only a speculation. All we can say is that, though each sector of the resonator models has its own pitch level, the actual formula which determines these pitch levels is not known. The determination of the exact formula is a point of academic interest only, but the demonstration of the actual existence of these pitch levels by means of the models is of prime importance, as furnishing an illustration of the resonance mechanism of the cochlea. It is possible that one other factor has to be reckoned with, namely impedance, which signifies a graduation of the loading of the basilar fibres by variation in the amount of friction to which the fluid columns are subject. This is a factor whose importance in determining the pitch of musical instruments has received considerable attention in recent years. Professor Roaf has suggested that it may be equally important in the tuning of the various pitch levels of the cochlea.

What does the resonance doctrine imply? In order to clarify our conceptions I think we require a few precise definitions. What, for instance, is a musical tone? It is usually defined as "a sound produced by regularly recurring waves of a definite frequency." This is no definition, for our recognition of a musical sound is quite

apart from any knowledge we may possess of its physical properties. *A musical sound is a sound of recognized pitch.* How then do we define pitch? If we consult our sensations, *pitch is position in a series.* It is only this fact which enables us to combine musical sounds in significant patterns which we call melodies. Our sense of pitch corresponds exactly to the physical fact of its being due to the excitation of a small group of nerve-endings *at a particular level of the cochlear scale.* Our sense of the relative pitch of two notes is more accurate than our sense of absolute pitch. We recognize the distance separating an octave, a fifth, or a third, as being the same in whatever part of the scale it occurs. It seems to me that our perception of the identity of musical intervals should imply a corresponding equal spacing of pitch levels on the cochlear scale. A compound musical tone we sense as a fundamental pitch, accompanied by a number of "harmonic components," which the trained ear is able to identify. The only mechanical arrangement which is able to resolve a fundamental and its harmonics is a series of resonators, such as we find in the cochlea, which it does by spacing them in a regular pattern on the basilar scale. *A noise corresponds to an irregular disturbance*, or "fuzzy patch," spread over a more or less wide area, but without a well-defined location *on the basilar scale.*

512 d.v. 400 d.v. 364 d.v. 256 d.v. 200 d.v.

FIG. 6.—Photographs of series of reactions obtained in the models in response to tuning-forks of various frequencies.

It is usual to regard the sense of hearing as perhaps the most mysterious of all our senses. I do not think this is so. I think we know a great deal more of the sense of hearing than of any other sense. Our knowledge of the physics of vision is fairly complete, and the photographic camera provides us with a mental picture recognizably analogous to the eye, but the analytical sense—i.e., colour vision—is still a matter for speculation; there is little groundwork of ascertained fact. On the other hand, the resonance mechanism of the cochlea is capable of demonstration as a physical reality, or, at all events, a physical possibility. About the other senses we know even less. As to the actual mode of action of the end organs of touch, or of thermal sensation, we know nothing. Smell and taste we recognize as being excited by chemical substances in solution, but as to how we distinguish the various qualities of those sensations we know absolutely nothing. Of the vestibular sense, on which such an immense amount of brilliant experimental work has been expended during recent years, the investigators themselves admit that the results arrived at remain baffling, inconsistent and enigmatical.

Though our acceptance of the resonance doctrine should do much to dispel the

legend of mystery which has clung so long to the cochlea, it will do nothing to lessen, rather will it enhance, our sense of its beauty. I recognize that appeals to æsthetic fitness are out of place in a scientific discussion, but after having indicated the rational basis of the resonance doctrine, one may spare a moment to contemplate and admire the beauty of what is surely one of the most consummate mechanical devices in Nature.

Section of Electro-Therapeutics.

[*April* 11, 1930.]

The Physiological and Cytological Effects of Penetrating X-rays upon the Cat and Rabbit.

By S. Russ, Samson Wright, H. A. Bulman, and L. H. Clark.

(Barnato-Joel and Physiological Laboratories, The Middlesex Hospital.)

Table of Contents.—(I) Introduction.—(II) Experimental Conditions.—(III) Physiological Symptoms following Irradiation.—(IV) Changes in the Organs produced by X-rays.—(V) The Rôle of Infection.—(VI) X-ray Sickness and Histamine Poisoning.—(VII) Blood Changes produced by X-rays.—(VIII) X-ray Anæmia and Liver Feeding.—(IX) General Discussion.—(X) Appendix.

(I) Introduction.

Three years ago experiments were begun on the physiological actions of comparatively small doses of X-rays on cats. In this work we were initially assisted by Dr. Morrison, now of the Glasgow Royal Cancer Hospital.

Numerous experiments were done to ascertain whether there were any easily recognized physiological effects subsequent to, or simultaneous with, applications of X-rays. The main things attempted in this direction were to see whether there were alterations in blood-pressure, respiration and in the threshold of sensory nerves to stimulation. The method of testing the latter was to expose the various nerves by dissection under anæsthesia, to determine the threshold stimulus and to continue such observations subsequent to exposure to X-rays.

A large number of kymographic records were made, but it was found extremely difficult to be sure that any of the effects were really due to the radiation itself. In view of these uncertainties this type of observation was suspended, without, we hope, being abandoned. We agree with other observers that the immediate effects recorded by Swann [1] are not really due to X-ray action.

The chief aim of the present experiments has been to discover the main physiological effects which result from the exposure of the cat and rabbit to somewhat heavy doses of X-rays.

(II) Experimental Conditions.

Types of Radiation employed.—Two groups of wave-lengths have been used, one a group within the limits 0·24 to 0·2 Å.U. from a Coolidge tube under induction coil impulses, giving a peak voltage of about 150 kilovolts, and the other a practically homogeneous beam of wave-length 0·16 Å.U. from a metalix tube under constant tension conditions, working at 230 kilovolts. The high tension source in this case was a high tension transformer with mechanical rectification, giving practically steady voltages up to a maximum of 250 kilovolts. This apparatus was the gift of Mr. Walter Butcher, to whom we are indebted for generous support in these and other researches. A brief description of this machine is given as an Appendix.

In these experiments, whichever group of wave-lengths was used, the general method of exposure of the animal was the same. When the animal was irradiated it was placed in a wooden box with a thin ventilated lid, and submitted to X-rays from above.

Determination of Lethal Dose.—The first thing was to find the minimum dose of radiation, which would certainly, or almost certainly, kill the animal.

The following table shows how this dose was reached for the *cat*, Section A

referring to exposures made with the coil set, and Section B to those made with the constant tension set.

Table I. (A.)

Duration of irradiation in terms of T_1	Number of animals used.	Survived.	Died.
1·1 T_1	2	—	2
0·74 T_1	2	—	2
0·55 T_1	7	—	7
0·45 T_1	10	3	7
0·36 T_1	2	1	1
0·28 T_1	2	2	—
0·22 T_1	2	2	—

Table I. (B.)

Duration of irradiation in terms of T_2	Number of animals used.	Survived.	Died.
0·26 T_2	2	0	2
0·21 T_2	2	0	2
0·18 T_2	7	0	7
0·16 T_2	1	1	0
0·11 T_2	1	1	0

The doses of radiation are expressed in terms of the times T_1 and T_2 required to produce, with the respective X-ray units, a lethal action (*in vitro*) upon the cells of the Jensen Rat Sarcoma, placed at the same distance from the X-ray tube as the floor of the box containing the animal.

From the figures in the table it may be concluded that a dose between 0·45 T_1 and 0·55 T_1, say 0·5 T_1, with the coil set was almost certain to kill a cat weighing about 2 kilograms, the whole animal being irradiated. With the constant tension set the corresponding dose is about 0·18 T_2. The ratio of the times required to kill a cat with the coil and with the constant tension set is

$$\frac{0{\cdot}5\ T_1}{0{\cdot}18\ T_2} = \frac{2{\cdot}8\ T_1}{T_2}$$

nearly three times the ratio of the times required to produce a lethal action upon the J.R.S. with the respective sets. In the case of the cat then, considerably less radiation of the shorter wave-lengths is required to produce a lethal action than is to be expected from the relative actions of the two beams on J.R.S.

Nature of Studies carried out.—The cats used in these experiments were selected of weight approximately 2 kilograms. In some cases the animals were killed, so that the intermediate stages of tissue damage could be studied. In general it may be said that the minimum killing dose for a cat causes a series of physiological effects of increasing severity leading to death.

Generalized doses give rise to so many effects that one cannot say which are the most likely to cause death without experiments of an eliminating kind.

As will be seen later, the chief damaging effects have been found in—(1) certain elements of the circulating blood; (2) intestinal tract; (3) kidney and liver; (4) bone marrow.

The following types of eliminating experiment have been tried:—

(*a*) Irradiation of the thorax only, the rest of the body being screened. In this way the abdominal viscera and most of the bone-marrow were spared. The exposures were prolonged so as to subject the circulating blood to as large a quantity of radiation as when the whole animal was exposed.

(*b*) Screening all parts except the abdomen and giving to this part of the body the same dose as it got under the conditions of generalized radiation.

(*c*) Screening the animal by means of a lead belt placed so as to protect the kidneys and adrenals.

(*d*) Screening the animal except for the long bones, thus giving the marrow heavy doses.

By such means, as will be discussed more fully below, information was obtained as to the importance of injury to various parts of the body in producing the total effect.

(III) Physiological Effects following Radiations.

Symptoms following Irradiation.—(1) *Cat* (severe cases). These are vague and indefinite; the animal seems little disturbed immediately after irradiation, but will not take all its food the same evening. The anorexia shows some fluctuations but usually becomes increasingly marked, and after the third day the animal usually leaves practically all its food and can only with great difficulty be persuaded to take a little milk or fish. Vomiting is not usually present and diarrhœa is rare (at death the small intestine is found to be empty and the large bowel contains some solid fæcal material). The skin may feel dry and stiff and the mucous membranes may be pale. There is rapid and marked loss of weight. One animal took practically no food or drink for 12 days and lost 40% of its initial weight. Recovery may, however, occur after a period of inanition of this duration. It seems surprising that the animal can manage without fluid for so long a time; Lusk [2], however, points out that the cat only sweats from the pads of the feet and that the water lost thus and in the urine and breath is made up by the water resulting from the oxidation of tissue substance. In the later stages the animal is dull and quiet, walks with difficulty and tends to stagger and collapse; finally it lies semi-conscious in its cage. External hæmorrhages from the mouth and nose are not uncommon. If pulmonary complications supervene the breathing may be rapid and laboured; otherwise it is slow and quiet.

(2) *Rabbit.*—There is no anorexia and the animal eats well, though there is slight loss of weight. In the one animal that succumbed there were no obvious symptoms till the day preceding death.

(IV) Changes in the Organs.

It is proposed to deal with the changes in the following organs: small intestine, stomach, large intestine, liver, kidney, spleen, respiratory tract.

As the anorexia and marked loss of weight were such outstanding features of the clinical picture in the cat, an especially detailed study was made of the changes in the alimentary canal.

Alimentary Canal.—The description is based on a study of the results of the irradiation of the whole animal and on the results of the additional experiments summarized below.

Region exposed.	Duration.	No of animals.	Died.	Killed.
Abdomen alone	0·55 T_1	7	2 (7th and 9th day)	5 (3rd to 8th day)
,, ,,	0·33 T_1	5	—	5 (5th to 8th day)
Abdomen alone (with adrenal region screened by means of broad band of lead 2 in. wide placed round abdomen).	0·55 T_1	2	1 (5th day)	1 (5th day)
Whole body except limbs and head.	0·55 T_1	1	—	1 (2 months after)

Speaking generally, when the abdomen is given a dose of 0·33 T_1 or less, the changes in the alimentary canal are very slight and almost wholly limited to

the small intestine. When the dose is increased to 0·45 T_1 and especially if it is increased to 0·55 T_1 the changes in the alimentary canal are striking and widespread. The small intestine again is most affected and is regularly involved. The stomach is involved less markedly and not invariably, the changes in the large intestine are less definite still, while the œsophagus is only occasionally affected. To determine the earliest type of change, it is essential that the animal be examined immediately after death or, better still, killed with coal gas—a method particularly valuable for bringing out slight congestion.

The changes observed are somewhat localized—for areas which appear normal may be contiguous with severely involved areas; this is difficult to account for but may be due in part to the way in which the coils of the intestine lay in the abdomen during the irradiation. The external changes are much less definite than the internal, as the mucous membrane is much more susceptible than the muscle coat. As a rule, too, microscopic examination reveals that the changes in the mucosa are more severe than is suspected from the naked-eye examination.

Small Intestine.—After dose of 0·33 T_1 or less, the changes noted are slight. There may be slight patchy congestion, and when it is marked the region of the mucosa is usually covered with a considerable amount of muco-purulent bile.

Microscopically, parts of the mucosa show enormous amounts of mucus in both villi and glands. In some of the mucous cells, curious darkly stained bodies are present; a few dilated capillaries and some cellular infiltration may be noted. In places the tubular epithelium may be shed.

With an exposure corresponding to 0·45 T_1, or 0·55 T_1, very severe destructive changes are observed which form a striking contrast to the slight changes just described. Changes are visible on the third day and are usually patchy, some coils escaping completely. The duodenum is fairly regularly involved, the change often starting sharply at the pyloro-duodenum junction. The mucous membrane is thickened and in places deeply congested. The lumen may contain a large amount of bile-stained mucus, and Peyer's patches may be enlarged and congested. The congestion does not affect the muscle coat, and externally the intestine appears normal.

Microscopically the changes found are greater than anticipated; congested areas regularly show considerable alteration in the glandular tissue of the mucosa. The *duodenum* shows an excessive amount of mucus in the lining cells of the villi, cellular infiltration is present between the gland tubules; in Brunner's glands in the submucosa the nuclei may disappear. Many widely dilated capillaries are present in the mucosa. In the *ileum* and *jejunum* the lining of the villi may be normal or only show nuclear change; but the deeper glands show desquamation of the lining cells and even complete disorganization of the tubules (fig. 1). Numerous polymorphonuclear cells are sometimes present. The stroma is increased in amount and preparations stained with van Gieson show that considerable fibrosis is beginning.

On the sixth to the seventh day a greater extent of the mucosa is involved. The congestion is greater; petechial hæmorrhages may be present or even patches several inches long covered with altered blood. There is much brown mucus in the lumen. In places the mucosa is rough and greyish white, or smooth and of a dead white colour.

Microscopically very extensive destruction is evident. Thus in the white patches referred to no villi are present, the mucosa is very thin and covered by a layer of cellular exudate. One specimen showed almost complete disappearance of all epithelial elements, leaving a fibro-cellular framework only (fig. 2); van Gieson preparations show extensive fibrosis. In the hæmorrhagic areas the disorganized mucosa contains many dilated capillaries and is covered by a layer of blood-clot

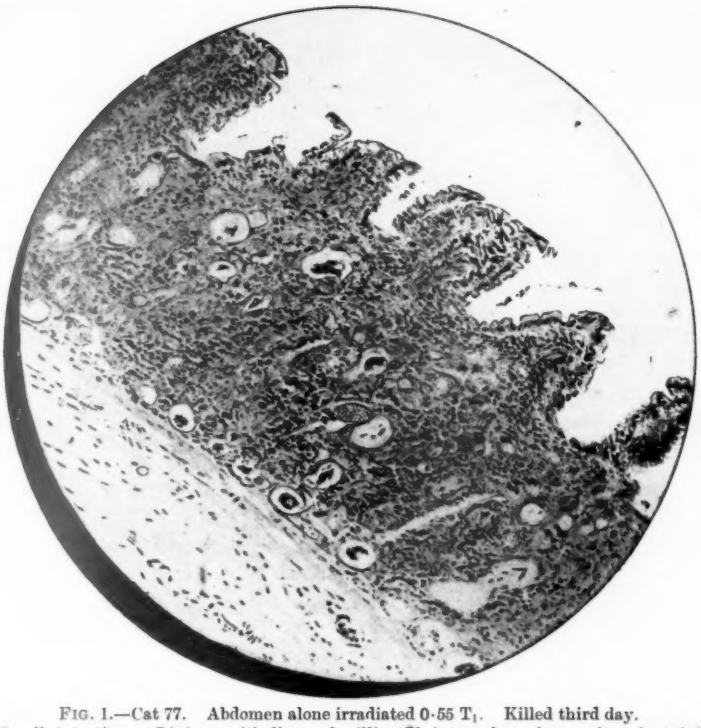


FIG. 1.—Cat 77. Abdomen alone irradiated 0·55 T_1. Killed third day.
Small intestine. Lining epithelium of villi still intact but shows altered staining characters. Subepithelial connective tissue contains many dilated capillaries. Epithelium of gland tubules is completely shed and in places contains débris of desquamated cells.

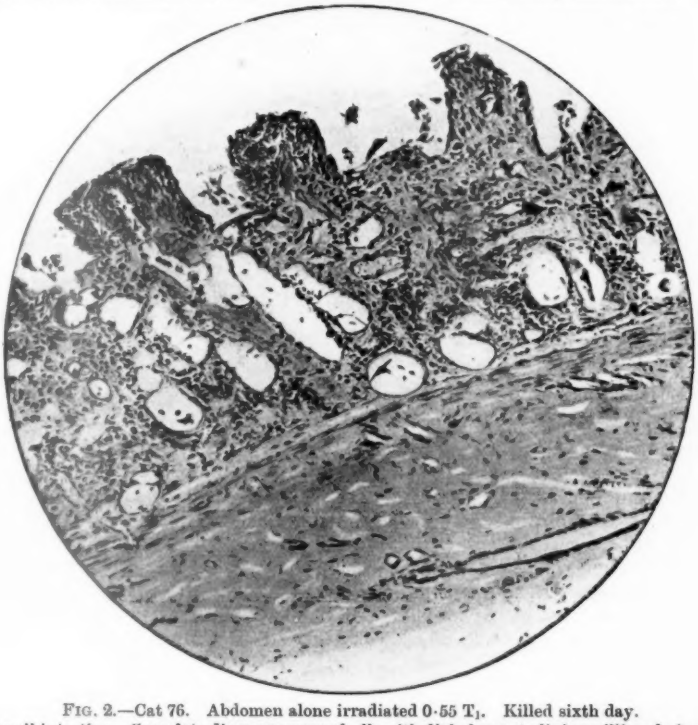


FIG. 2.—Cat 76. Abdomen alone irradiated 0·55 T_1. Killed sixth day.
Small intestine. Complete disappearance of all epithelial elements lining villi and gland tubules. Connective tissue framework is intact. Fibrosis is commencing.

containing many leucocytes (fig. 3). In the less affected areas the villi, which are intact, are lined by cells which stain faintly and show irregular nuclei; in places the tops of the villi are necrosed or completely shed (fig. 4). The gland tubules show various degrees of change, up to complete destruction. The outlines of the cells become vague, the nuclei break up, the cells are shed and spaces are found containing débris and leucocytes.

Many bacteria, both Gram-positive and Gram-negative, are often found in the most affected regions; this infection appears to be secondary to the destructive changes described, and is only obvious in the most affected regions.

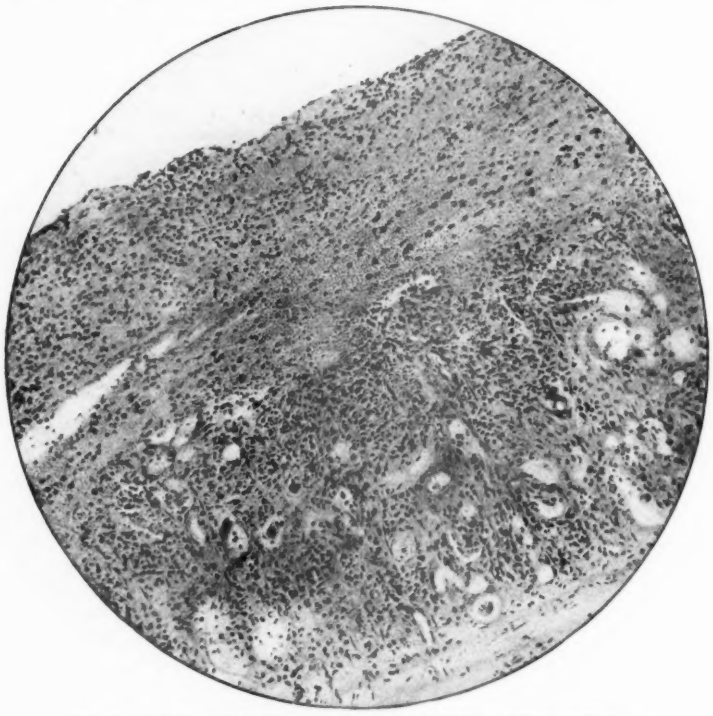


FIG. 3.—Cat 76. Abdomen alone irradiated 0·55 T_1. Killed sixth day.

Small intestine. Villi completely disappeared. Surface of mucous membrane is covered with hæmorrhagic membrane containing numerous leucocytes. Tubular epithelium is shed. Considerable infiltration of stroma with leucocytes.

In some of the most advanced cases (eighth to ninth day) external congestion is seen. The muscle coat is in places very limp, in others it shows heightened irritability and contracts vigorously for a long time in response to mechanical stimulation. In addition to the usual changes, the mucosa is in places green in colour, obviously necrotic and peeling off. The sub-mucosa and muscle coat in such regions are thickened and œdematous. Hæmorrhages are sometimes found involving the whole thickness of the intestinal wall. *Microscopically* there is ample evidence of infection—great polymorphonuclear infiltration and numerous bacteria. The mucosa is completely absent, in places revealing either lymphoid tissue or the muscle

FIG. 4.—Cat 21. Whole animal irradiated 1·1 T_1. Died.
Small intestine. Disappearance of villi. Desquamation of lining of many tubules. No leucocytic infiltration of stroma.

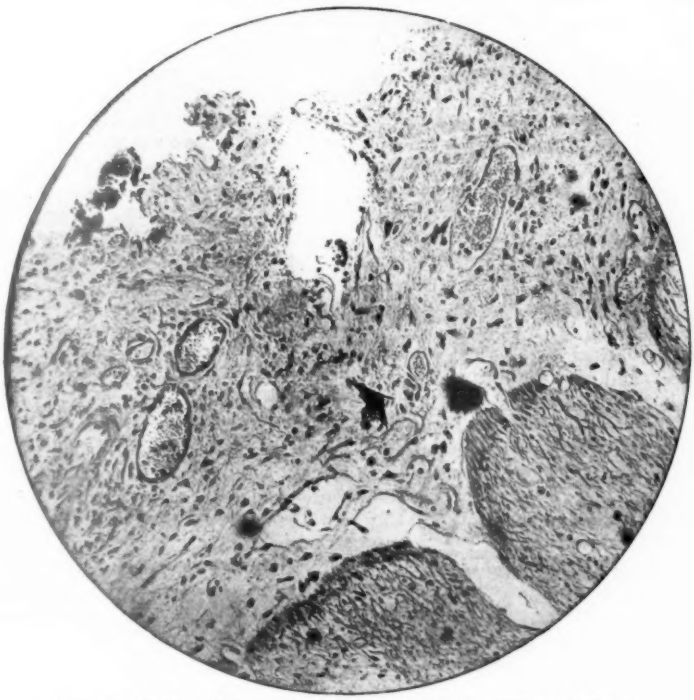


FIG. 5.—Cat 74. Abdomen alone irradiated 0·55 T_1. Killed eighth day.
Small intestine. Mucous membrane is completely shed, leaving ragged submucous coat which is intensely congested. Muscle coat shows hyaline changes.

coat covered by remnants of the submucosa or with a layer of exudate (fig. 5). There is intense capillary dilatation in the submucosa and the muscle coat may be hyaline.

The changes which have been described may be summarized thus: (1) *Vaso-dilatation* involving the mucosa first and spreading outwards, accompanied by exudation of fluid (œdema) and of polymorphonuclear cells and sometimes by microscopic or macroscopic hæmorrhages. It should be noted that when the leucocytes in the circulating blood are markedly reduced following appropriate irradiation of the whole animal, polymorphonuclear invasion of the mucosa does not occur. Apart from this difference the changes in the intestine are essentially the same, whether the abdomen alone or the entire animal is irradiated, except that the lesions tend to be somewhat more severe in the latter cases, presumably owing to a lowering of the resistance; (2) destruction of the epithelial elements lining the villi and tubules; (3) proliferation of the connective tissue leading to fibrosis or (4) infection resulting in extensive necrosis.

Stomach—The changes in the stomach tend to be more marked at the pyloric end; the cardiac end may escape irradiation in cases where the abdomen alone is irradiated because of its position under the ribs, which were screened with lead. Following a dose of 0·33 T_1 the naked-eye changes are slight; congestion is rarely obvious and macroscopically the mucous membrane may appear normal; in some instances the deeper gland cells may stain poorly, their outline may be vague, and some cellular infiltration may be present. Following a dose of 0·55 T_1 naked-eye changes may be apparent on the third day, when patches of the mucosa may be deeply bile-stained. *Microscopically* the deeper glands of the pylorus are found in places to have lost their lining, while the cells lining the glands may be dead or desquamated. There is a degree of polymorphonuclear infiltration and some fibrosis. Evidence of infection of the damaged areas is usually lacking.

On the sixth to the eighth day considerable congestion of the pyloric end is often visible to the naked eye, and microscopically many dilated capillaries are seen in the mucosa. The changes in the mucosa are more extensive, but usually limited to the deeper parts; the superficial epithelium and ducts tend to be intact. The deeper glandular epithelium may be shed in places; elsewhere the nuclei are pyknotic and surrounded by a clear halo of non-staining cytoplasm. The thickness of the mucous membrane may be reduced. When changes are noted at the cardiac end they too tend to involve especially the deeper parts of the mucosa. The cytoplasm of the parietal cells stains progressively less well. The parietal cells may completely disappear when the chief cells are less involved, but in places the tubules are completely disintegrated.

In one animal (killed sixth day) the stomach showed multiple erosions (where the mucous membrane had disappeared) surrounded by a red, raised edge. In more severe cases marked hæmorrhages are present, involving the whole thickness of the gastric wall, and the stomach contains much coffee-coloured material; or parts of the mucosa may be shed and replaced by a membranous exudate.

Large Intestine.—Changes have only been noted following doses of 0·55 T_1; these are much slighter than those observed in the small intestine. This may occasion surprise when one considers how closely the epithelia and glands in the two regions resemble one another. To the naked eye there is congestion of the mucosa. Microscopically the changes are of the same general nature as those in the small intestine, but milder.

Liver.—Following a dose of 0·22 T_1 the liver shows congestion and fatty infiltration of a patchy character, which is more severe and extensive after doses of 0·45 T_1 to 0·55 T_1. Many liver cells contain fat globules, or the whole cytoplasm is replaced by fat, with the result that the affected region of the liver resembles adipose tissue. Numerous microscopic patches of focal necrosis are present, scattered irregularly

throughout the organ; here débris of the liver cells may be visible and a certain amount of cellular infiltration.

Similar changes were noted when the liver alone was irradiated and the rest of the body was screened; these changes can thus be produced directly by the X-rays, and are not necessarily secondary to changes (e.g. infection) in other parts of the body.

Following a dose of 1·1 T_1 extensive areas of necrosis are noted, and the surviving cells are separated from one another by considerable amounts of connective tissue.

It is worth pointing out that an animal which had a dose of 0·22 T_1 and received intensive feeding with liver extract and whole liver, showed extensive necrosis round the central veins.

Kidney.—The changes are relatively slight. Following a dose of 0·55 T_1 there is some cloudy swelling of the epithelium of the convoluted tubules, desquamation of the lining in places or exudation into the lumina. In the medulla the loops of Henle may show some desquamation. No cellular reaction has been noted.

These changes are sometimes observed when the abdomen alone is irradiated and in the absence of infection.

Spleen.—This showed the characteristic changes described in other species by previous observers—namely, diminution or almost complete disappearance of the lymphocytes in the Malpighian corpuscles and in the pulp, and a condensation of the fibrous tissue. There was evidence of increased phagocytosis of red cells and occasionally slight siderosis.

Respiratory Tract.—This was studied in three animals, in which the thorax was given doses of 1·9 T_1, 3·0 T_1 and 3·5 T_1 respectively. The detailed findings were as follows:

Cat No. 1, *Dose* 1·9 T_1—Killed on the twenty-seventh day. Lungs crepitant, but reddish in colour.

Sections.—The epithelium of the trachea and large bronchi is no longer ciliated columnar but cubical. There is degeneration of the alveolar walls in places with breakdown leading to an emphysematous condition. Patchy areas of hæmorrhagic and œdematous infiltration of alveolar lumina. Slight broncho-pneumonia is present.

Cat No. 2, *Dose* 3·0, T_1.—Killed on the twenty-fifth day. Scattered over the surface of the lungs are triangular areas of a fibrous character, slaty in colour. Adjacent to some of these are red consolidated areas about 2 mm. deep.

Sections: Alveolar walls thick from proliferation of endothelium; small areas of hæmorrhage. The appearance is suggestive of diffuse repair of old patches of necrosis. The mucous glands of bronchi are degenerate and the epithelium is desquamated. There is some peribronchial infiltration.

Cat No. 3, *Dose* 3·5 T_1.—Died on the seventh day. Both lungs deeply congested, markedly œdematous, with small and large, dark red and black consolidated patches. Trachea is patchily congested and contains frothy fluid.

Sections: Intense engorgement of lungs with hæmorrhages. Small foci of inflammatory changes; congestion and degeneration of the glands.

When the lungs alone were given a dose of 0·55 T_1 no definite changes were observed. The lungs are frequently the seat of secondary infection. Pulmonary abscesses and empyema are not infrequently a terminal feature in fatal cases.

Organ Changes in the Rabbit.—Though these resembled in general the changes found in the cat, certain differences were obvious.

In the *stomach* the naked-eye changes are greater and more regular than in the cat, and more extensive than those in the small intestine. Thus, a rabbit, in which the abdomen was given a dose of 0·33 T_1 and killed on the sixth day, showed an area of deep purple congestion in the vicinity of the cardia, and there were white patches of superficial necrosis of the mucosa. The congestion was quite

evident in animals killed on the third or fourth day. After a dose of 0·55 T_1 the congestion may involve the whole of the interior of the stomach, and, as the stomach contents are washed out, large flakes of the dead mucosa often come away. In spite of these advanced changes, the animals took their food well, did not lose weight, and generally speaking the stools were well formed. Microscopic examination confirmed the results of naked-eye inspection, and showed extensive necrosis of the superficial parts of the mucosa. In another rabbit given a dose of 0·55 T_1 and killed on the third day, the glandular tissue in the pyloric region was almost completely destroyed, and the mucosa reduced to a fibrous stroma covered by a structureless membrane. There was, however, no evidence of infection.

The changes in the *small intestine* are of the same general nature as those in the cat, but less marked. Macroscopically, congestion of mucosa and (sometimes) of the muscle coat are the only changes observed. Speaking generally, the destruction of the epithelial elements (surface and glandular cells) is not so extensive as in the cat, though in places it is severe. Hæmorrhage is rare, and again infection was absent. The large intestine was little involved.

In the *liver* the changes were very slight, except when very heavy doses of radiation were given. In a rabbit which died following irradiation of the whole body with a dose of 1·1 T_1 the liver was bright yellow in colour, spongy and very friable. Almost all the hepatic cells were necrosed and the bile-duct epithelium was injured. The sections showed numerous large spaces containing débris of disintegrated liver cells and numerous anaerobic organisms. This infection was probably a terminal or even a post-mortem phenomenon. In only one animal given a dose of 0·55 T_1 were definite changes noted; these consisted of slight focal necrosis, degenerative changes in the pericentral cells and superficial hæmorrhages.

The *kidney* was frequently involved. Small hæmorrhages, glomerular congestion and tubular changes, e.g., desquamation of lining cells, especially in medulla, and presence of casts were noted in many cases after doses of 0·33 T_1 to 0·55 T_1.

The *spleen* showed the usual decrease in lymphocyte content, and siderosis was a fairly regular feature.

The lungs were not affected, except in the case of a rabbit given a dose of 1·1 T_1. In this case patches of consolidation were present.

(V) The Rôle of Infection.

In many of the fatal cases in the cat the most striking post-mortem feature was the presence of infection, especially in the lungs, where pneumonia, abscesses and empyema were frequently observed; sometimes blood-culture proved positive without definite localization of the infection in any particular organ. The changes observed in the lungs are sometimes so gross that it might be thought that the rays had produced an initial necrosis on which an infection was secondarily superimposed. The view that an initial necrosis is set up in the lung is negatived by the fact that the lung is highly resistant to the action of the rays. Thus in the case of a cat in which the lungs received a dose of 1·9 T_1 the structural changes noted were quite slight, and consisted mainly of breakdown of the alveolar walls in places, and some infiltration with fluid and cells. A dose of 0·55 T_1 is unlikely, therefore, to produce significant changes in the lungs. In the description of the intestinal changes, however, attention was drawn to the extensive injury of the epithelial elements, the more advanced lesions showing signs of infection. The infection seems almost certainly to be of a secondary nature, because extensive injury is frequently unaccompanied by bacterial invasion. When the whole animal is irradiated there is little evidence of tissue reaction to the local bacterial invasion. The organisms may get into the blood-stream, and owing to the altered state of the blood they proliferate and settle in the various organs, which may account for their presence in the lung.

(VI) X-ray Sickness and Histamine Poisoning.

It has been shown by Lewis [3] and his co-workers that radiations and other agencies which injure the skin cause the liberation of histamine or of a histamine-like substance ("H" substance). It appeared possible that some of the symptoms following penetrating doses of radiation might result from the absorption of such a body in considerable amounts from skin or other tissues. A study was therefore made of the effects of injecting histamine acid-phosphate subcutaneously in various doses over a period of time. To produce any symptoms very much larger doses must be given by the subcutaneous than by the intravenous route. Thus 3 mgm. produces no obvious effects; 9 mgm. usually produces vomiting; following 18 mgm. the animal is very sick, the pupils are widely dilated, there is some narcosis and solid food is not touched for some hours. There is flushing of the mucous membrane of the nose, the conjunctivæ, the ears and of the pads. When doses of 15 to 30 mgm. are given several times daily at intervals of three to four hours, a condition of chronic ill-health is gradually produced. The appetite is lost, there is rapid loss of weight, lethargy, depression and great muscular weakness, and death finally results. One animal died on the fifth day after receiving 250 mgm., another on the ninth day after receiving 640 mgm. A third animal died more rapidly, on the third day after receiving only 30 mgm.

The effects upon the blood of cats subjected to subcutaneous injections of histamine have been studied. In one case when 24 mgm. were injected at intervals, the chief change in the leucocyte count was an increase in the polymorphonuclear elements, the numbers of the lymphocytes diminishing. In another case a single injection of 30 mgm. was followed by a decline in the leucocyte count, the cat dying in 48 hours.

The detailed effects upon the blood of the cat subjected to a series of injections of 24 mgm. of histamine were as follows: Two hours following the first injection the total count was 35,000 compared with a highest count during the control period of 18,000; the polymorphonuclear cells numbered 29,000 (highest control 9,000), and formed 74% of the total. Another injection was given; five hours from the start the total count was 53,000, and the polymorphonuclear cells constituted 90%. In this experiment the total count was not maintained at this high level, though the injections were repeated; it fluctuated, being lowest in the morning after the time allowed for recovery in the night, and rising again in consequence of the renewal of the injections. The polymorphonuclear percentage, however, remained high throughout. The lymphocytes tended to decrease in absolute numbers down to 1,000 to 2,000 per c.mm. The increase in the total white count might be attributed to concentration of the blood, for histamine is known to increase the permeability of capillaries and cause exudation of fluid from the plasma into the tissue spaces. This view is at once negatived by the fact that the increase is in polymorphonuclear cells and does not affect the lymphocytes. Dale [4] has found that intravenous injections of histamine produce an immediate decline in the total leucocyte count.

The general clinical picture of histamine poisoning somewhat resembles that of X-ray sickness in so far as both lead to progressive weakness, emaciation and death. Vomiting, however, is not a feature of X-ray sickness in the cat, and the blood-changes are quite dissimilar.

(VII) Blood Changes produced by X-rays.

A very extensive series of observations has been made upon the effects of the X-rays used in these experiments upon the elements of the circulating blood. It is unnecessary to record these observations here completely; for with regard to the action of X-rays on the circulating lymphocytes and polymorphonuclear leucocytes, no important differences have been observed distinguishing the cat from

other animals. Almost inevitably after a comparatively heavy dose of penetrating X-rays, the blood is practically free from lymphocytes, and at a later stage from polymorphonuclear leucocytes. Whether there is a subsequent return to the normal count depends upon two things. One is the magnitude of the dose of X-rays given, and the other the various organs irradiated. It has been found that, while recovery from a heavy generalized dose is comparatively rarely seen, yet when certain parts of the animal are protected the recovery may be complete. These two effects are illustrated in figs. 6 and 7. Fig. 6 shows a very lengthy recovery after a dose which

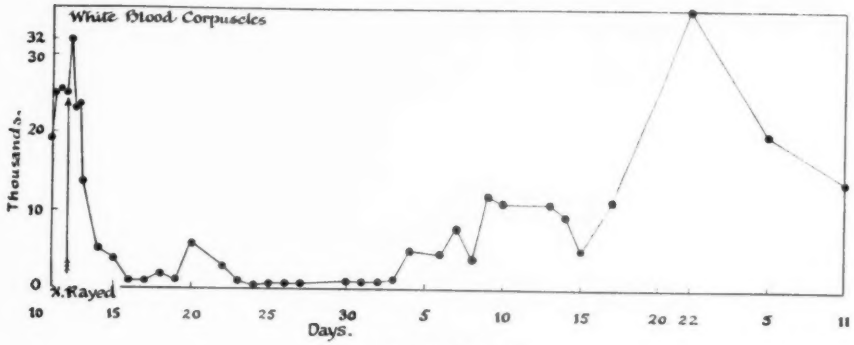


FIG. 6.—Irradiated 0·45 T_1.

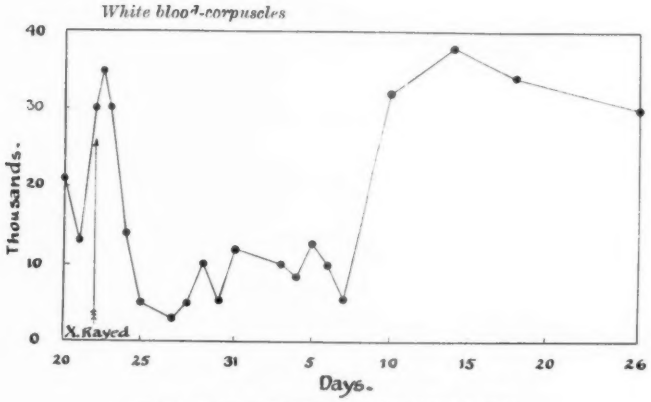


FIG. 7.—Chest and abdomen. Irradiated 0·55 T_1.

was very near the lethal dose for the whole animal. Fig. 7 shows the comparatively rapid return to the normal count in spite of a considerable riddance of the circulation of its leucocytes : in this case a localized dose to the thorax and abdomen was given.

The blood observations emphasized in this paper are those upon the red cells and the platelets. When cats had been given a heavy generalized dose of X-rays which led to their death, it was found that very severe damage had been done to various parts of the alimentary tract, and in cases of this sort, blood observations were made previous to the death of the animal. A typical case is exhibited in fig. 8, which is

a record of blood-counts on a cat which had been given a dose of 0·45 T_1. Whereas the leucocytes are practically withdrawn from the circulation, it is seen that the effect on the red cells is small except just before the end, and on the platelets even less, though this particular animal, at the time of its death, was found to be suffering from extensive lesions of the small intestine, which were the seat of bacterial

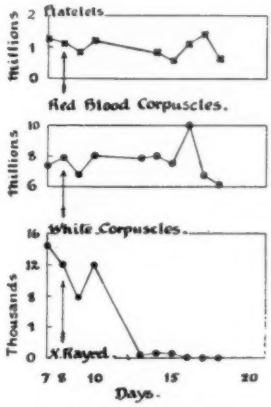


FIG. 8.—Irradiated 0·45 T_1.

invasion; yet at the time of death the platelet count was not sensibly different from what it was before the animal was X-rayed. An experimental finding like this makes it very difficult to suppose that, in the cat, the circulating blood-platelets play a controlling part in defence against bacteria.

(VIII) X-RAY ANÆMIA AND LIVER FEEDING.

An attempt was made to determine to what extent the anæmia which follows sublethal doses of irradiation to the whole animal could be controlled by the administration of liver, in view of its remarkable action in the treatment of pernicious and secondary anæmia. The animals were offered half a pound of liver daily, of which a varying amount was consumed, depending on the animal's general condition. If it was not eaten, it was supplemented by the administration of a concentrated fluid extract in amounts of about $\frac{1}{2}$ oz. daily. Five animals were used in this study. Two were submitted to doses of 0·05 T_2 from the constant tension set and three each received a dose of 0·22 T_1 from the coil set.

In all cases a definite anæmia developed, so that the liver treatment failed as a preventive measure. It had been hoped that, even should liver fail to prevent the development of anæmia, it might hasten the restoration of the blood to normal. There was no opportunity of studying this point because four of the animals died, although none received doses of radiation which were lethal to animals *not* receiving liver. Post-mortem examination of the four animals that died showed most extensive and multiple hæmorrhages that appeared to be the immediate cause of death. Animals which have been given similar amounts of liver and which have *not* been irradiated have so far not shown this remarkable and wholly unexpected result.

As this series of animals produced such unforeseen results a further series was undertaken. Four cats were each given a dose of 0·07 T_2 to the whole body.

Two were fed on liver diet (8 oz. of liver and ½ oz. of liver extract daily) whilst the remaining two were fed on normal diet (cat's meat, fish, etc.). On the twelfth day after irradiation one of the liver-fed cats refused to eat, the extract being forcibly introduced. It died on the fourteenth day. The post-mortem examination showed extensive and multiple hæmorrhages. The other liver-fed cat appeared to be losing weight on the fourteenth day; it was carefully watched and observed to be suffering from melæna. It was sacrificed on the nineteenth day after irradiation. Although the post-mortem examination did not show such a striking picture as did that of another liver-fed cat, there was indubitable evidence of hæmorrhages from the intestines, more especially the large intestine. The control animals were alive and well two months after irradiation. Another cat, which was not irradiated, but was placed on the liver diet, was also alive and well eight weeks after beginning the diet.

(IX) General Discussion.

When the evidence which has been presented is reviewed, it is clear that the X-rays produce degenerative changes in all the tissues which are exposed to their influence, and the change may be sufficiently severe to lead to the death of the cells. Besides these parenchymal changes in the organs, vascular reactions occur —vasodilatation, especially of the minute vessels, exudation of fluid and even hæmorrhage.

The question naturally arises whether the radiations act directly on the tissues, or through the intermediary of some chemical agent which they produce. The experiments which we have carried out with histamine are opposed to the view that this substance is the responsible agent in X-ray sickness. Histamine was selected for examination because it (or something closely similar) is believed to be liberated when certain tissues are injured in other ways. We have found, however, that repeated injections of histamine, even in doses which finally prove fatal, do not give rise to the characteristic intestinal changes, and the changes in the blood differ from those seen following X-rays. It must be admitted, however, that were the X-rays to liberate histamine, it would be formed in the affected tissues, and might act differently under those conditions from the way it does when it is absorbed from the skin. At the moment, however, it seems more probable to suppose that the radiations directly disturb the metabolic processes of the cells in such a manner as may lead to their ultimate death. The view that has been expressed that the tissue damage is due to infection does not seem likely, because the destructive changes may be obvious prior to the occurrence of infection. There is marked difference in the relative sensitivity of the different organs in any one species. Thus, in the cat, the small intestine and spleen are most readily affected, the stomach and large intestine come next, then the kidney and liver. The lungs are much less vulnerable and are only directly damaged by very heavy exposure.

There are further differences in the degree of sensitivity of any one organ in a number of species. Thus, in our experience, the small intestine and the blood-forming organs appear to be definitely less vulnerable in the rabbit than in the cat.

Our work has shown that the general effects of irradiation in a species depend not only on the quantity of irradiation employed, but also on how much of the body is exposed, and particularly on which organs are subjected to radiation. In the cat the sequence of events, when a minimum lethal dose is given to the whole body, appears to be somewhat as follows:—

Very extensive degenerative changes in the mucosa of the small intestine; it becomes vulnerable and is invaded by the organisms that normally reside in the bowel lumen. These organisms complete the destruction which has already been

inflicted directly by the rays. The mucosa may completely slough away, leaving the deeper vessels and lymphatics exposed to bacterial invasion. Organisms enter the blood, and at this stage *B. coli* may be cultured from the circulating blood. The effects produced by the bacteria depend on their number and virulence and on the power of resistance of the body. The animal is enfeebled by starvation, itself largely the result of the alimentary changes; it is considerably dehydrated from loss of fluid which is not wholly made good; the chemical composition of the blood appears to be altered—in our experiments there was a definite and fairly regular decrease in the plasma chloride and in some instances a slight alkalæmia. It is reasonable to suppose that the tissue cells may be bathed by a fluid which is not the optimum. In addition, when the whole animal is irradiated, the white cells almost completely disappear from the circulating blood, probably partly owing to a direct action of the rays on the blood-stream, and partly to a destructive action on the myeloid tissues in the bone-marrow and spleen. The resistance of the animal is almost certainly lowered, with the result that the organism settles in various organs —especially the lungs, setting up inflammatory changes (abscess, pneumonia, empyema) which bring on the fatal issue. The damaged areas in the stomach and the large intestine offer additional avenues for infection and contribute also to the general alimentary derangement.

Cramer, Drew and Mottram [5] have drawn attention to the frequency with which infection takes place in rats given heavy doses of gamma radiation. They find that this is associated with a marked decrease in the platelet count; they appear to suggest that the thrombopenia is partly primary and that this decreases the resistance of the animal to infection, and that when bacterial invasion occurs, a further decline in the platelets takes place which is due to their being used to agglutinate the organisms. As pointed out, we have failed to notice any correlation between the blood-platelet count and the development of infective states in the cat.

The changes in the kidney are slight; those in the liver are more definite but are only severe (and involving considerable areas of liver) when the period of irradiation is prolonged. It is difficult to assess to what extent they contribute to the general clinical picture, because one must always bear in mind the enormous functional reserve which is present in these organs; further, it is more important to know how much the surviving cells can do than to note the number which have been destroyed. Bearing on this point is the fact that when the liver alone is given a dose of 0·55 T_2 the animal's health appears to be little disturbed. Derangements of renal and hepatic function would therefore appear to be of merely subsidiary importance.

Attempts have been made to test various functions by means of acute experiments when the symptoms are well marked. These have not been very successful because the animal readily succumbs during the administration of the anæsthetic or during the preliminary operative procedures—thus affording further proof of the general debility of the animal. In the few instances in which further observation could be made the blood-pressure was found to be low and respiration depressed; nervous excitability did not seem much altered.

When the abdomen alone is irradiated with the minimum lethal dose the animal sometimes survives. Irradiation of the thorax, the head or the limbs with the same dose produces little general disturbance of importance; in some cases (thorax) apparently on account of the high degree of resistance of the organs, in others (bone-marrow of limbs) because other parts function vicariously and so compensate for the injuries which have been inflicted.

Very heavy irradiation of the abdomen or thorax (3·5 T_1) may produce enough severe local injury finally to lead to death.

In the *rabbit* a dose of radiation lethal for the cat produces much less severe changes in the small intestine, though considerable inflammatory and ulcerative

changes may occur in the stomach. With such doses of irradiation the white count does not fall below the order of several thousand per c.mm. The state of the appetite and nutrition, it has been pointed out, also remain quite good. These features, combined with the less severe intestinal involvement, may account for the greater resistance displayed by the rabbit. In the one animal that died hepatic failure appeared, histologically, to be a decisive factor.

In a study upon the effects of gamma rays upon the tissues in animals (rat, rabbit and cat) Lazarus-Barlow [6] came to the conclusion that late or secondary changes after gamma radiation are largely hæmal in origin. On the other hand, he considered that the primary changes in cells as the result of this kind of irradiation are physico-chemical. In contrasting the effects of gamma rays upon the rabbit with those seen in the rat and cat, he mentions that mucoid degeneration of cells, quite apart from the formation of goblet cells, is much less intense in rabbits.

Radio-Therapy.—Inferences drawn from experimental observations on the lower animals may or may not apply to the human subject, but if they are valid in the present instance, the obvious inference is that the gravest consequences may result from heavy doses of penetrating radiation to the normal tissues. It has long been known that patients sometimes suffer severely after heavy doses of X-rays; here the issue is complicated, because the patients are not in normal health, and any disturbance set up in the body by the X-rays may well be accentuated. The general symptoms and course of X-ray sickness in man have been summarized by Sir Humphry Rolleston [7]. This form of sickness has not, we believe, been traced in any detail from its physiological beginnings, but its general features are more like than unlike what we have observed in the cat. Damage to vulnerable but healthy tissue, destruction of circulating blood-cells, hindrance to blood production by the marrow, and the onset of bacterial infection are all likely to have the gravest consequences if they occur in a patient being treated with penetrating X- or gamma-rays. Our observations appear to show that radiation damage to fixed tissue cells is a more likely precursor to the onset of bacterial infection than is the temporary removal of a very large percentage of leucocytes in the circulating blood; the latter deficiency is soon made good if the marrow has not been badly damaged, but damage to the intestine, stomach or lung tissue is not easily made good.

The striking differences in vulnerability shown by different portions of the intestinal tract of the cat are difficult to account for on purely histological grounds, and it may be that the function played by the different parts is of equal importance in determining the degree of reaction to the rays. It may be reasonable to suppose that the difference in susceptibility of the cat and rabbit is to some extent due to their widely different diets. The experiments on the liver feeding of X-rayed cats described in this paper suggest that further study of the effects of different diets during and after X-ray treatment might help in alleviating X-ray sickness and even worse conditions.

(X) Appendix.

The constant tension X-ray unit.—This X-ray unit was built to deliver a current of 10 ma. at a constant tension of 250 kilo volts. This output is obtained by the mechanical rectification of the three-phase high tension alternating currents delivered by two identical transformer units, which are shown diagrammatically as A and B in fig. 9. It will serve therefore to describe one of these transformer units, say A.

The step-up oil-immersed transformer has three primary windings connected end to end and three secondary windings, which all meet in a common insulated

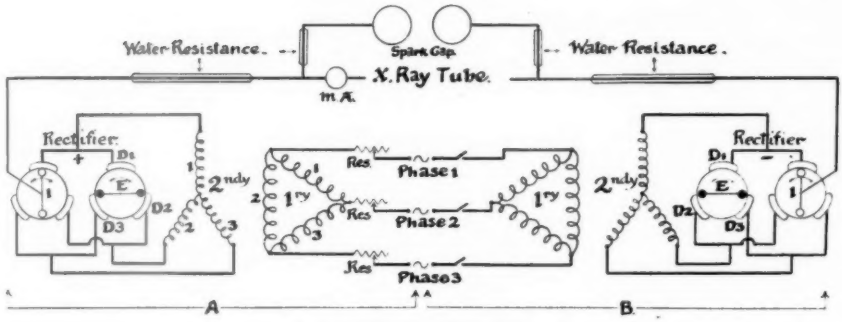


FIG. 9.—Constant high-tension unit.

point. Three alternating currents, differing in phase by 120°, are fed into the three primary windings from a three-phase alternator, which also serves as the synchronous motor driving the mechanical rectifier. The output of the machine is determined by the strength of the currents in the primary windings, and these are controlled in two ways. The first control is a potential divider in the field circuit of the alternator, by which the output of the latter may be varied. The second is shown in the figure, and is a variable resistance placed in series with each primary winding, with a means whereby all these resistances are varied equally and simultaneously. The frequency of the alternating currents is read on a frequency meter placed in parallel with one of the primary windings, and is controlled by a variable resistance placed in the field circuit of the motor which drives the alternator.

The free ends of the secondary windings of the transformer each terminate at the sector of a special mechanical rectifier, which is the novel feature of this machine.

The rectifier has three insulated stationary sectors, and each sector is made in duplicate (*vide* fig. D1, D2, D3), the horizontal distance between the two portions being 36 cm. There are two revolving collectors, I and E, to the rectifier, in the form of two straight metal arms placed at right angles to each other, 36 cm. apart. One arm, I, is insulated and revolves in the plane containing the three sectors, whilst the other rotates in the plane of their duplicates and is connected to earth. Only the current flowing to the insulated arm is utilized and is fed through a brush contact to the metalix X-ray tube.

This disposition of the rectifier is such that the two collectors are always collecting current from different secondary windings of the transformer. The rectifier is adjusted so that the insulated collector always receives current from the secondary windings, when the maximum potential difference is being generated in them, whereas the voltage of currents picked up by the earthed arm is always comparatively low. The net result is that the wave-form of the potential generated by the machine shows a maximum variation of only 4 to 5%.

Only one-half of the X-ray unit has so far been described. Two such units, A and B, are employed to produce a steady output of 10 ma. at 250 kv. The three primary windings of one unit are placed in parallel with the three corresponding windings of the other unit, each to each. The electrical connections between the two units are such that the potential of the insulated collector arm of one rectifier is positive to that of the other. Before reaching the metalix X-ray tube the currents from the two rectifiers pass through water resistances which tend to eliminate surges.

The filament of the X-ray tube is fed from a 12-volt bank of large capacity secondary cells, which is very heavily insulated. The current through the tube is measured by a milliamperemeter, and the voltage operating across it is measured by means of a sphere gap in parallel with the tube, having spheres 25 cm. in diameter. A subsidiary check on the voltage operating is afforded by the readings of voltmeters placed in parallel with each of the primary windings of the transformer.

REFERENCES.

[1] SWANN, M. B. R., *Brit. Journ. of Radiol.*, 1924, xxix, 195. [2] LUSK, G., "Science of Nutrition," 4th ed. Philadelphia, 1928. [3] LEWIS, Sir THOMAS, "Blood Vessels of Human Skin and their Responses," London, 1927. [4] DALE, H. H., Unpublished Communication. [5] CRAMER, DREW and MOTTRAM, *Proceedings of the Royal Society*, B, 1922, xciii, 449. [6] LAZARUS-BARLOW, "Medical Uses of Radium," *Medical Research Council Report*, Special Report Series, No. 62, 1922. [7] ROLLESTON, Sir HUMPHRY, *Brit. Med. Journ.*, 1927 (ii), 9.

Section of Urology.

[*April* 30, 1930.]

The Advantages of the Perineal Route in the Treatment of Various Diseases of the Prostate.

By HUGH H. YOUNG, M.D., D.S.M., F.R.C.S.I.

(*Professor of Urology, Johns Hopkins University and Hospital, Baltimore*).

WHEN I received the invitation of this Section I cast about for a suitable subject, and it seemed to me that if I were to discuss some of the various surgical procedures which I have carried out through the perineum, and stress the advantages which the perineal route seems to offer for certain operations upon the prostate, it might be of interest. I do not come here to insist that perineal prostatectomy should be adopted to the exclusion of the suprapubic method. The splendid work done by the late Sir Peter Freyer and his co-workers and others in London and elsewhere in Great Britain, has so greatly impressed the world with the results which can be obtained by suprapubic prostatectomy, that these methods have been adopted, almost to the exclusion of others, in many parts of the world. I hold no brief against suprapubic prostatectomy, but in the rejoicing over the great boon which has been conferred by operation through the suprapubic route, the profession has often overlooked the advantages of the perineal route as a method of approach, not only for benign hypertrophy, but for various other conditions of the prostate, which can hardly be satisfactorily attacked except through the perineum.

One of the principal reasons why the perineal route became so unpopular was that for many years a median perineal incision was used. In this the operator plunged his knife into the urethra, through the central portion of the perineum, traversed the bulb, the external sphincter and its surrounding muscles, and in so doing occasionally cut into the rectum. Serious hæmorrhage often occurred, and not infrequently incontinence of urine resulted. In addition to this, the deeper intravesical portions of the prostate were often left behind, with resultant recurrence of obstruction.

A glance at the anatomy shown in these slides demonstrates at once that the prostate may easily be reached without injuring the surrounding structures. It is only necessary to make the incision so that the region behind the bulb, the triangular ligament, and the external sphincter may be reached directly, and the prostate attacked under visual inspection.

With the development of prostatic hypertrophy, not only is the urethra usually flattened from side to side, but the middle lobe projects upward into the urethra —to the bladder—adding to the obstruction. With this there is seen a progressive hypertrophy of the trigone. I have shown in studies upon the anatomy and physiology of the trigone, that one of its principal offices is to pull down the posterior

portion of the prostatic orifice, and thus open the internal sphincter for the egress of urine; in fact, micturition is initiated by contraction of the trigone, which opens the external sphincter and allows the detrusor muscles to force the urine out through the urethra (fig. 1). When obstruction occurs at the prostatic orifice, it becomes increasingly difficult for the trigone to open the internal orifice, and, as a result, it becomes progressively hypertrophied, so that one frequently sees a very great muscular enlargement of the trigone, as is shown in fig. 2. Often, with no enlargement of the prostate to be felt *per rectum*, or to be seen with the cystoscope, the presence of a hypertrophied trigone will give the clue to hidden obstruction, often intra-urethral in character. This correct explanation of the physiology of micturition and the important part played by the trigone, has not yet been recognized by physiologists.

One advantage of operating upon the prostate through the perineum is that excellent anæsthesia may easily be obtained by a single injection of 20 c.c. of 3% procain into the sacral canal. By this simple means perfect anæsthesia, with excellent relaxation, is obtained, not only for the region of the perineum and rectum, but also for the deeper portions of the prostate and seminal vesicles. Since many patients requiring operation upon the prostate are not fit subjects for general anæsthesia, the advantage of this simple sacral method is obvious.

In passing, I may say that I believe many of the difficulties encountered by operators attempting to reach the prostate through the perineum have been due to an imperfect position of the patient. I have seen operators work upon a flat table, and with such a poor exposure of the perineum that they were not able to obtain a good view of the operative field. It is not only necessary that the perineum should be elevated, but the pelvis should be bent forward at the sacro-iliac joint. By means of a special table and accessory apparatus, I have been able to obtain an excellent position for proper exposure of the perineum.

With the patient in the proper position the incision should be made so as to avoid unnecessarily injuring important structures and to give a proper exposure for careful operation. In most cases a curved incision, the sides of which are parallel to the ischio-pubic ramus, and the centre of which is about 3 cm. in front of the anterior margin of the anus, gives the best exposure. After dividing the skin and fascia, it is possible, by simply pushing the index finger into the fatty tissue on each side of the central tendon, to open up the space behind the transversus perinei muscle on each side. By simultaneous use of the handle of the scalpel we can quickly determine if we are behind the transversus perinei muscles and the triangular ligament. This is very important, because, if we should make this primary dissection in front of these muscles we would then come down upon the anterior surface of the triangular ligament, and if we proceeded further, would greatly injure the complex musculature forming the external sphincter. A bifid tractor is then introduced, and the median tendon is placed on tension and divided well behind the bulb (fig. 3). As the deeper regions are approached, one is careful to recognize the rectum and avoid it. The recto-urethralis, which runs from the rectum to the membranous urethra (fig. 4), is then brought to view by blunt dissection on each side, picked up with forceps near its juncture with the membranous urethra, and divided. This immediately frees the rectum and opens up the space between it and the membranous urethra, and the apex of the prostate, which may be easily disclosed by gentle blunt dissection with the handle of the scalpel. In most cases traction with a specially devised bulb retractor which encircles the urethra, draws the sphincter and Cowper's glands downward, and presents an elongated thoroughly membranous urethra, where it joins the apex of the prostate. A median urethrotomy is usually made with the scalpel upon the sound previously introduced into the urethra (fig. 4 b), the incision being made so as to include portions of the prostatic urethra, thus avoiding injury to the external sphincter. Through the edges of the urethra,

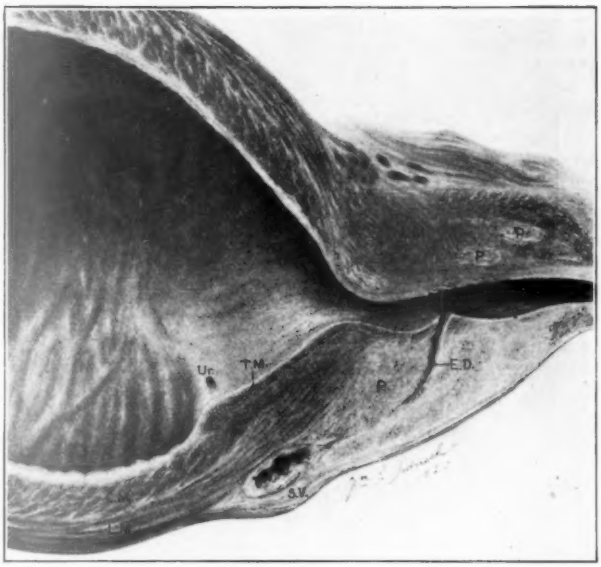


FIG. 1.—Sagittal section through bladder and urethra in median line. The trigonal muscle is shown running down beneath the vesical orifice into the urethra. When this contracts the urethral orifice is pulled downward and opened.

FIG. 2.—Sagittal section in case of prostatic hypertrophy, with considerable enlargement of lateral and median lobes. The prostatic orifice was irregularly dilated. Incontinence of urine. Trigone markedly hypertrophied with pouch behind it.

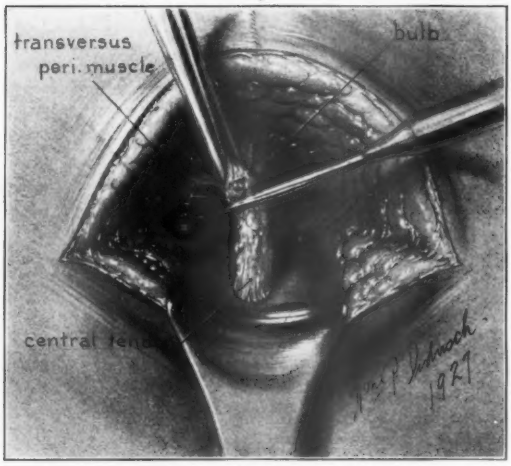


FIG. 3.—The bifid tractor pulls the rectum back, stretching the central tendon which is being divided by a scalpel.

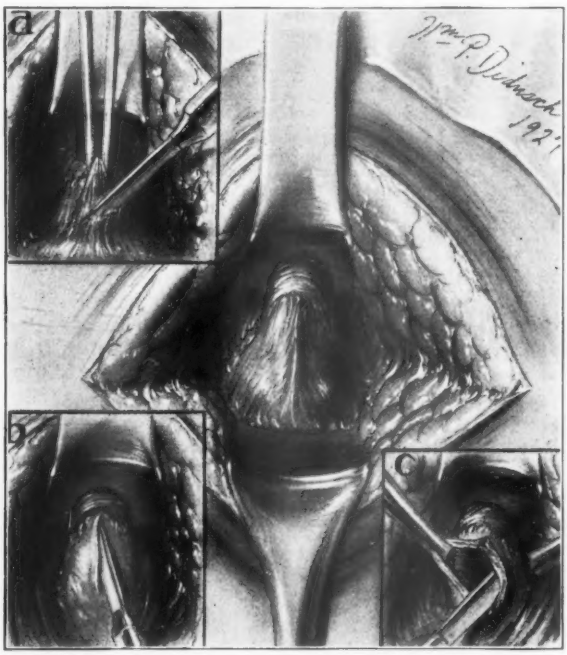


FIG. 4.—The bulb retractor has been introduced and traction made, exposing the external sphincter and the recto-urethralis muscle which extends from the rectum forward along the posterior surface of the membranous urethra. In (a) this muscle has been picked up and has been divided close to the urethra and well away from the rectum, after which the urethra and apex of the prostate are freed by blunt dissection, the rectum being pushed backward. In (b) the urethra is opened in the membranous urethra behind the external sphincter upon the sound in the urethra. In (c) the edges of the mucous membrane are caught up with forceps, the scalpel assisting in elevating each side preliminary to catching it with Allis clamps.

held apart by Allis clamps, my prostatic tractor is introduced into the bladder (fig. 4 c), opened out, traction made, and the posterior surface of the prostate exposed. After dividing the delicate fibres which form the posterior layer of Denonvillier's fascia at the apex of the prostate on each side, one recognizes the anterior layer of Denonvillier's fascia by the pearly-white appearance where it covers the prostate (fig. 5). If the operator recognizes this, and follows it upward, there is never any danger of injuring the rectum, and an excellent exposure of the posterior surface of the prostate, and even of the seminal vesicles above, is thus obtained.

The technique which I have described is applicable in the great majority of operations which one may be called upon to employ for pathological conditions of

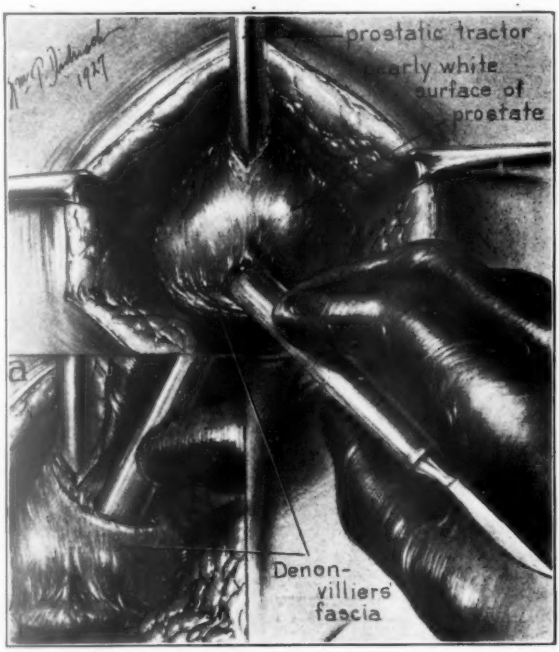


FIG. 5.—Posterior surface of the prostate is almost completely exposed, after stripping back the posterior layer of Denonvillier's fascia (a).

the prostate and seminal vesicles through the perineum. One can bring the prostate and seminal vesicles up, see what one is doing, palpate, resect, have frozen sections made, and indeed carry out careful, open, thorough, and accurate surgical work; the method being, in all these respects, certainly far superior to the suprapubic approach. One reaches the prostate, which is an extravesical organ, directly, and not after violating the bladder twice.

Having thus drawn down and exposed the prostate, the surgeon may use any type of incision in cases of prostatic hypertrophy that his fancy dictates. At first I

employed a transverse incision, in which I enucleated in one piece the hypertrophied lateral and median masses. For a long time I employed a bilateral capsular incision, through which the two lateral and median lobes were removed separately, with preservation of the verumontanum, ejaculatory ducts and urethra. I have also employed an inverted " V " incision (fig. 6), through which the adenomatous lobules may be removed in one piece (figs. 7 and 8), with or without the adjacent anterior commissure, thus giving a specimen almost identical with that produced by the

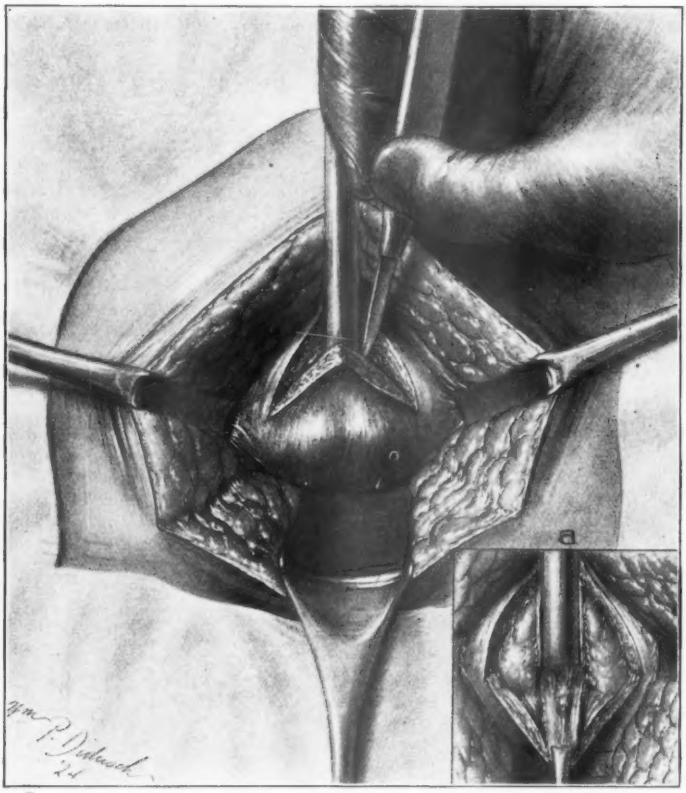


FIG. 6.—Young's prostatectomy through an inverted " V " capsular incision. In (a) the lateral walls of the urethra are shown divided, and the posterior flap is drawn backward exposing the floor of the urethra verumontanum and hypertrophied lateral lobes.

Freyer suprapubic technique, in which the lateral and median portions of the prostate, bound together with the anterior commissure, come away in one lobular mass. In most cases it is preferable not to remove any of the anterior commissure, the extirpation of lateral and median portions being entirely radical, but when the anterior commissure contains definitely adenomatous masses this portion should also be included. In the majority of cases I have used the bilateral

incision, but the objection to this is that one cannot remove the hypertrophied lobes in one piece, as by the inverted "V." It is more conservative, however, than the inverted "V" technique, there is less injury to the urethra, the perineal wounds heal more quickly, and there is less likelihood of injuring the sexual function, but the exposure obtained is not so good, the adenomatous mass is not removed in one piece, and occasionally adenomatous lobules have been left behind.

Not infrequently small calculi are present, usually between the hypertrophied lobes and the capsule. If such cases are recognized beforehand, a bilateral capsular incision is usually preferable, in that one may remove with a curette or spoon the numerous calculi which are present beneath the lateral and median lobes, as shown

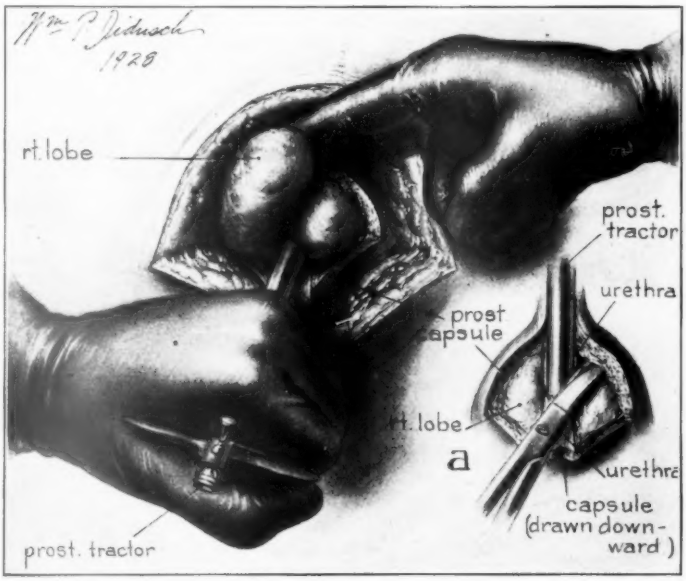


FIG. 7.—Enucleation of lateral lobes through inverted "V" incision. In (a) the inverted "V" flap of posterior capsule and urethra is pushed backward, while with enucleating scissors the enucleation of the left lateral lobe is begun. In the central figure enucleation has progressed until the right lateral lobe is almost completely drawn out, being held only by its attachments with the median lobe, which connects the two lateral lobes behind the prostatic tractor.

in fig. 9. It is almost impossible to remove such calculi when suprapubic technique is employed. Calculi in the bladder may easily be removed through the dilated vesical orifice left by the removal of the hypertrophied lobes. In a few cases the calculi have been 4 or 5 cm. in diameter. In several instances the calculi are attached to cellules, or are within the orifices of the ureters, but little difficulty has been experienced in satisfactorily grappling and removing them through the perineum. I do not, however, recommend this method in such cases.

Having removed the prostate and stone through an inverted "V" incision, one is prepared to carry out whatever closure may seem desirable. In a good many cases we have used the technique by means of which the mucous membrane

at the vesical neck is drawn down and sutured to the tissues at the apex of the prostate; this is somewhat similar to the technique which Dr. Wildbolz has demonstrated here. The advantage of this technique is that hæmorrhage is checked; it is necessary only to employ a urethral catheter for about a week. In about 40% of our cases, primary healing, without any leakage through the perineum, was obtained, but a careful study of our results seemed to show that there was more

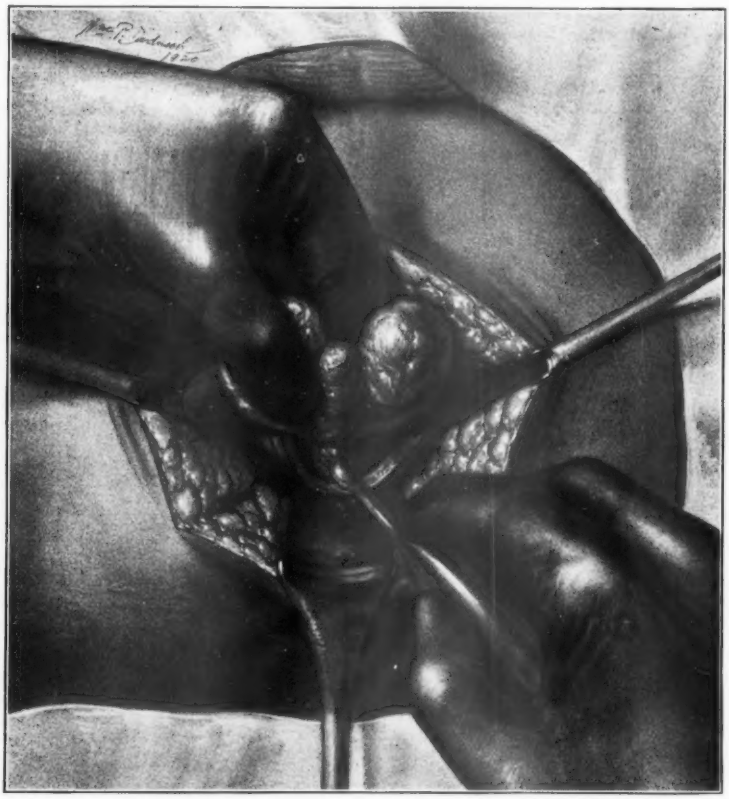


FIG. 8.—The tractor has been removed and the index finger of the left hand introduced through the vesical orifice into the bladder to investigate the median portion. The subtrigonal lobule has been discovered, and is being separated from the sphincter by the blunt tractor.

danger of suppuration, sepsis, embolic pneumonia, etc. We have, therefore, returned to a more open method, in which, after inserting a catheter in the urethra, the Davis drainage bag is introduced through the prostatic wound into the bladder and blown up, and traction is made, thus stopping all hæmorrhage, and at the same time affording additional drainage of the bladder. By means of the Davis bag all gauze packing is avoided, and the only prostatic sutures which we use are placed in one side of the wound to approximate the cut edges and restore the posterior flap to

its normal position. The levator ani muscles are then approximated to protect the rectum, and the wound is closed, generally in front and on one side, with the drainage tubes emerging from the other angle.

Such is the operation which we usually carry out in cases of benign prostatic hypertrophy. The specimen removed is often identical with that which one would obtain through a suprapubic incision, but the condition of the vesical neck after such removal is entirely different from that following suprapubic prostatectomy, in which very large lobes are drawn out through the internal sphincter, greatly dilating, or even completely destroying it, and leaving, as a permanent defect, a widely dilated funnel-like projection from the bladder into the posterior urethra, as shown in fig. 10. After perineal prostatectomy, however, especially when the lobes do not project greatly into the bladder, the internal sphincter is often not injured at all, and as a result it promptly contracts to normal after operation, as shown in the cystogram

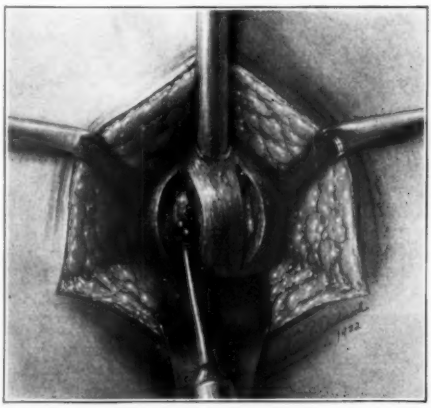


FIG. 9.—Lateral capsular incisions have been made, the calculi which are found in the stream between the lateral hypertrophied lobes and the posterior portion of the prostate being removed.

taken after perineal prostatectomy, (fig. 11, p. 74). Fortunately, dilatation of the internal sphincter rarely causes much inconvenience, and perfect urinary control is present, regardless of the fact that the prostatic urethra has become a part of the bladder.

In some cases, after suprapubic prostatectomy, when the removal has been more extensive, and particularly when the mucosa, and some muscle, have been removed from the membranous urethra, as shown in fig. 12, definite injury of the external sphincter may result, leading to complete incontinence of urine. A number of such cases operated on elsewhere have come to me for cure of the resultant incontinence. The same thing may happen after perineal prostatectomy, and for the same reasons; in fact, incontinence has been more common after perineal prostatectomy, but is usually caused by direct injury of the external sphincter during the operative approach to the prostate. This, however, should not occur, and is a distinct operative fault, due to failure to recognize the anatomical structures, and to avoid the muscles of the triangular ligament and membranous urethra, which are concerned in urinary control.

FIG. 10.—Widely dilated prostatic orifice following suprapubic prostatectomy with dilatation of the external sphincter and incontinence.

FIG. 11.—Cystogram after perineal prostatectomy. Internal sphincter normally closed.

To describe the results obtained by perineal prostatectomy, I append a table which gives the cause of death in 1,571 personally operated consecutive cases.

TABLE SHOWING CAUSES OF DEATH IN THE 58 MORTALITIES OCCURRING IN A CONSECUTIVE SERIES OF 1,571 PROSTATECTOMIES (3·6 PER CENT.).

Principal cause of death	No.	Per cent.	Principal cause of death	No.	Per cent.
Pneumonia	15	25·8	Hæmorrhage of nose ...	2	3·5
Uremia	7	12·0	Endocarditis	1	1·7
Pulmonary embolism ...	7	12·0	Abscess of spleen	1	1·7
Sepsis	7	12·0	Pulmonary tuberculosis ...	1	1·7
Heart disease	5	8·6	Extravasated urine ...	1	1·7
Cerebral hæmorrhage ...	3	5·1	Cancer of intestine ...	1	1·7
Acute pulmonary œdema	2	3·5	? Transfusion reaction ...	1	1·7
Cerebral thrombosis ...	2	3·5	? Adrenal disease... ...	1	1·7
Hæmorrhage of wound ...	2	3·5			
		Mortality ... 3·6%			

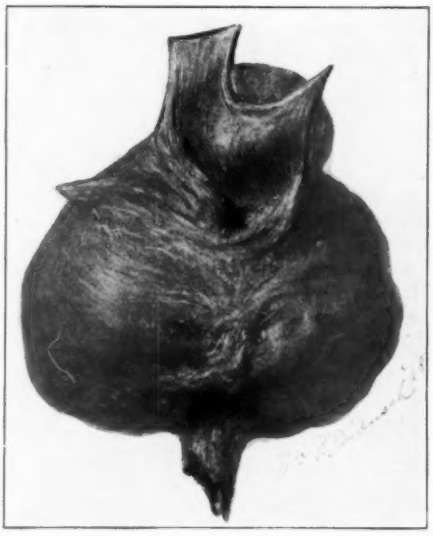


FIG. 12.—Hypertrophied prostate removed by suprapubic prostatectomy, in which the anterior commissure was enucleated with the lateral lobes, and a portion of the membranous urethra also came away, resulting in slight incontinence.

It will be seen that pneumonia and pulmonary embolism (which is also often responsible for the pneumonia) are the most important causes of death. Pulmonary embolism is the most baffling and inexplicable complication of all types of surgical operation. It is supposed usually to come from a femoral vein, but often one is unable to find any lesion within the vein, or any septic cause. It has been more common throughout the world in recent years, as shown by the extensive literature. Sepsis plays an important part, and for this, perineal drainage is very important, and accounts for the lower mortality, as evinced by the 3·6% which was obtained in these 1,571 cases. Although 50% of the cases have had some cardiovascular lesion, only 8% of the deaths can be attributed to a cardiovascular condition.

In my work during twenty years I have had a fluctuating mortality rate. Beginning with a rate of 8%, in three years it was reduced to zero, and there were 128 cases without a death. Then it rose to 5%, and then was again reduced and

remained at zero for two years. I have recently had, during a period of three years and six months, a series of 198 consecutive cases, in six of which the patients were over 80 years of age, and in 58, over 70.[1] This series of consecutive cases without a death shows conclusively that the operation *per se* is not a serious one, and it is only owing to the advanced age and the complications encountered that fatal cases occasionally occur. That the perineal route is unquestionably the safer, has, I think, been definitely proved. That both perineal and suprapubic prostatectomies are radically curative and technically satisfactory is undoubtedly true, as the specimen removed may be practically identical in both cases.

A not infrequent condition which is met with during prostatectomy is a fibrous contracture of the vesical orifice, and in such cases my punch operation may be performed (fig. 13) through the urethra to remove the fibrous bar, and sometimes to facilitate the enucleation of the deeper portions of the prostate.

A very important thing in prostatic surgery is the fact that about 20% of the persons who present themselves with symptoms of prostatic obstruction have carcinoma of the prostate. In about one-half of the cases there is present a definite benign adenomatous enlargement of the lateral and median portions of the prostate: in such cases carcinoma usually involves the posterior portion of the prostate, and may not yet have invaded the hypertrophied lateral and median lobes, which may be enucleated suprapubically, and fail to demonstrate the carcinomatous involvement on pathological examination. When the prostate is attacked through the perineum, however, that portion of the prostate which is usually involved in carcinoma is reached first; one can generally make a diagnosis by palpation, or, if necessary, the nodule may be incised, and a frozen section made, and examined under the microscope. This, I take it, is one of the most important reasons why perineal prostatectomy is, as a surgical procedure, far superior to the suprapubic operation.

One should recognize carcinoma of the prostate on rectal examination, especially if the prostate is palpated with a cystoscope in the urethra, thus showing the peculiar increase in induration in the sub-urethral portion of the prostate, which is rarely seen

[1] Analysis of 198 Consecutive Cases of Perineal Prostatectomy without a Death—February 8, 1919 to October 15, 1922.

Ages		Residual urine		Blood-pressure		Phthalein		Blood-urea	
Years	No.	C.cm.	No.	P. B.	No.	%	No.	Gm.	No.
50—54 ...	13	0— 49 ...	40	100—109 ...	5	0— 9 ...	1	1·40—1·49 ...	1
55—59 ...	26	50— 99 ...	31	110—119 ...	12	10—19 ...	2	1·30—1·39 ...	1
60—64 ...	48	100—199 ...	37	120—129 ...	24	20—29 ...	10	1·20—1·29 ...	1
65—69 ...	50	200—299 ...	21	130—139 ...	29	30—39 ...	17	1·10—1·19 ...	1
70—74 ...	40	300—400 ...	11	140—149 ...	41	40—49 ...	36	1·00—1·09 ...	1
75—79 ...	12	500	4	150—159 ..	24	50—59 ...	55	0·90—0·99 ...	1
80—84 ...	6	600	6	160—169 ...	19	60—69 ...	46	0·80—0·89 ...	1
No information	1	900	1	170—179 ...	15	70—79 ...	14	0·70—0·79 ...	3
		1000	1	180—189 ...	10	80—89 ...	2	0·60—0·69 ...	2
		1200	2	190—199 ...	6	90—99 ...	1	0·50—0·59 ...	3
		1800	1	200—209 ...	2	No information	12	0·40—0·49 ...	10
		Compl. R. U.	12	210—219 ...	3			0·30—0·39 ...	16
		No information	29	No information	6			0·20—0·29 ...	20
								0·10—0·19 ...	6
								0·01—0·09 ...	1

Heart		Discharge		Fistula closure		Result on discharge	
Cases	No.	Days	No.	Days	No.		
Enlarged	34	10—14 ...	5	5— 9 ...	2	Well	165
Murmur	30	15—19 ...	12	10— 14 ...	19	Improved	25
Enl. and mur.	16	20—24 ...	40	15— 19 ...	53	No information	6
Myocarditis	16	25—29 ...	32	20— 29 ...	54		
		30—39 ...	56	30— 39 ...	19	Ultimate results:—	
Preliminary treatment	No.	40—49 ...	28	40— 49 ...	6	Cured	129
None	52	50—59 ...	9	50— 59 ...	8	Improved	10
Catheter continuous ...	100	60—69 ...	8	75— 79 ...	1	Not improved	1
Intermittent	6	70—79 ...	1	100—104 ...	1	No information ...	56
Suprapubic	4	Over 90 ...	6	Average 24 days		Deaths after 6 months	8
No information ...	34	No information	1			Deaths before 6 months	2

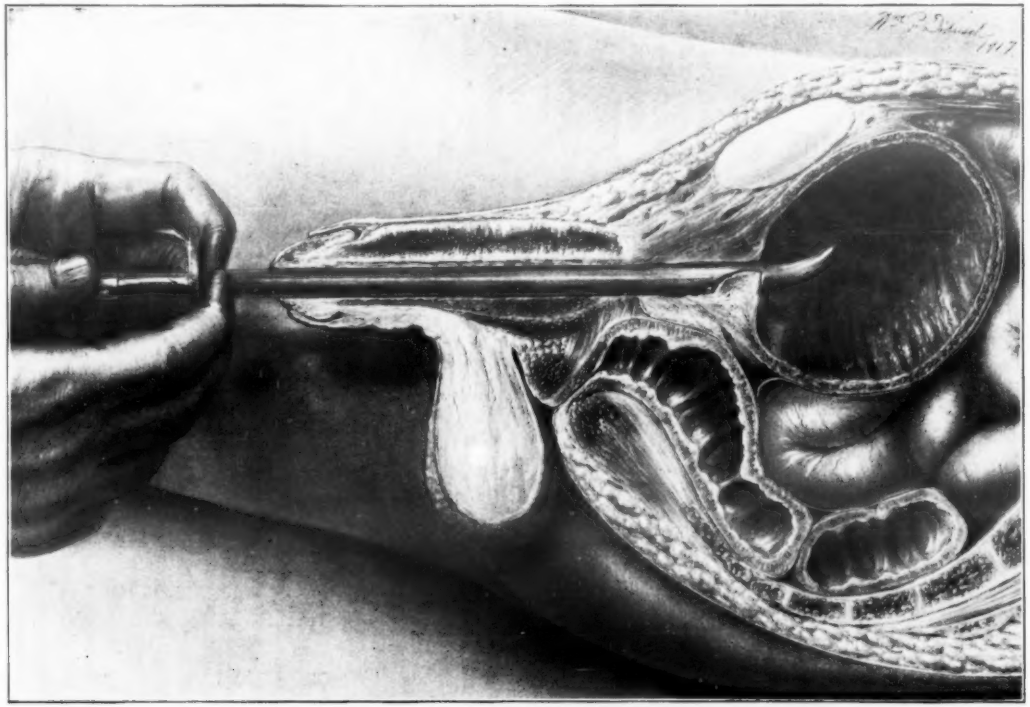


FIG. 13.—Young's Punch Operation. The outer tube has been withdrawn far enough to entrap the median bar in the fenestra, as indicated by a checking in the flow of fluid. The hands of the operator are shown ready to push the inner tube home.

in simple hypertrophy. If practitioners could be made to realize the importance of rectal examinations, and to suspect great induration of the prostate, even if localized to a small area, many more cases of prostatic carcinoma, sufficiently early for radical cure, would be detected.

When the disease has gone too far for radical cure, and when the obstruction makes operative relief imperative, I have employed, with great success, a conservative perineal prostatectomy, using the old bilateral capsular technique (fig 9), with resection of the lateral lobes, followed by resection of the median portion of the prostate through one of the lateral cavities. This operation has now been carried out in my clinic in about five hundred cases, with a mortality very little higher than in cases of benign hypertrophy, and with functional results which are usually excellent, and continue so, as long as the patient lives. Many of these patients live from three to six years after such operative removal of the obstructing portions of the prostate. An amazing thing is that they rarely develop intra-urethral carcinomatous growths. They die from metastases, but usually not from urinary difficulties. That such cases cannot be satisfactorily dealt with through the suprapubic route has been abundantly proved, and it is generally recognized that while, occasionally, carcinoma associated with hypertrophy is removed sufficiently completely to cure the obstruction, it can be removed much more satisfactorily and surgically through the perineum, which is undoubtedly the operation of choice in such cases. Where carcinoma and hypertrophy occur together, enucleation through the perineum of the hypertrophied lobes and the partial resection of the carcinomatous involvement usually suffice to give lasting functional results until the patient dies from metastases. Many patients live three or four years afterwards.

The Radical Operation for Carcinoma of the Prostate.—This should be carried out when a chance of complete cure is considered possible in a case of carcinoma of the prostate. The technique which I proposed in 1905 has now been carried out by me in thirty-one cases with results so satisfactory that I would like to dwell on some of its points. In the first case I carried out a new radical procedure, in which I cut across the membranous urethra, and removed the entire prostate, with its capsule, and urethra, the neck of the bladder, both seminal vesicles and a considerable portion of the ampullæ on each side in one piece. The defect was closed by anastomosing the wide open bladder to the stump of the membranous urethra.

In the first ten cases in which I employed this method there are several complete cures, and the results were excellent, except that all had incontinence of urine. In considering the causes of this, it seemed remarkable that the external sphincter should not function to give urinary control, especially in view of the fact that in many cases, after suprapubic prostatectomy with the wide open vesical neck and greatly dilated internal sphincter, the external sphincter alone provides satisfactory urinary control. Why should these patients, who still had the external sphincter left intact by the radical operation, have incontinence of urine ? Turning to the anatomy for an explanation, it seemed that the blood-vessels and nerves, which supply the region of the external sphincter and preserve its tone and function, were probably injured by the operation. Considering in detail the anatomical cross-section of this region (fig. 14), it seemed evident that if I had been careful not to penetrate the anterior fascia which comes in front of the prostate, it should have been possible to avoid injury to the blood-vessels and nerves which supply the external sphincter. Accordingly, during the next radical operation for carcinoma of the prostate, I determined to modify my technique so as to be careful to remain posterior to this anterior transverse prostatic fascia. It was found not only easy to accomplish this, but in so doing, hæmorrhage, which previously gave much trouble, was avoided, and the ultimate result was that complete urinary control and normal urination were obtained, regardless of the fact that the entire prostate, with its capsule, the vesical neck, the urethra and two-thirds of the trigone, had been removed

with the seminal vesicles, in one piece, as shown in figs. 15, 16, 17 and 18. The anastomosis between the wide-open bladder and the stump of the membranous urethra is simple and satisfactory, and since this improved technique was adopted sixteen years ago the mortality has been 4 per cent.—only slightly larger than that of benign prostatic hypertrophy cases—and urinary control has been obtained in most cases, in some of which it is not necessary for patients to rise even once at night to void urine. These cases show that when an appropriately radical procedure was carried out before the disease had progressed too far into the region of the seminal vesicles, and while it was still confined between the fascia which covers the prostate and seminal vesicles, a high percentage of cures could be obtained. The results are distinctly better than those obtained in carcinoma of the breast. The explanation of this lies in the fact that the prostate is so firmly surrounded by layers of fascia (the capsule propria and the fascia of Denonvillier) that the disease remains confined for a long time ; in fact, it rarely penetrates these fasciæ, but travels upward beneath them. That such results may be obtained makes it all the more imperative that we should teach the profession as a whole to carry out rectal examinations as a routine part of all physical examinations, and to suspect even

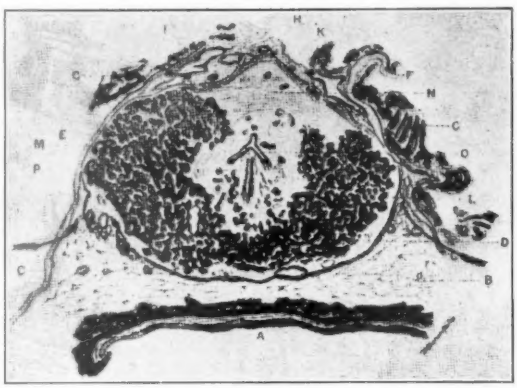


FIG. 14.—Transverse section of prostate and fascias surrounding it. Note the two layers anteriorly. By going in, as shown by the arrow, one may remove the prostate with its capsule without injury of the prevesical vessels and nerves.

small areas of great induration. In a good number of the cases in which I carried out my radical operation, the disease had indeed progressed too far to expect a cure. With the early recognition of carcinoma a high percentage of complete cures should be obtained by this radical procedure, which, of course, can only be carried out satisfactorily through the perineum.

Tuberculosis of the Prostate and Seminal Vesicles.—This is a condition in which surgeons as a rule have avoided—and in most cases actively combated—any idea of operative intervention. Such cases are usually associated with tuberculosis of the epididymis, and the procedure which has been universally adopted has been simple epididymectomy, with no attempt to remove the tuberculous involvement of the vesicles and the prostate. Several years ago, after a careful study of our cases in which epididymectomy had been carried out, I became convinced that the results thus obtained were very bad, and that in almost all cases there was involvement of the seminal vesicles and prostate, which continued to increase in severity, resulting in involvement either of the urethra and bladder or of the kidneys, eventually leading to generalized tuberculosis, from which the majority of these patients died. The

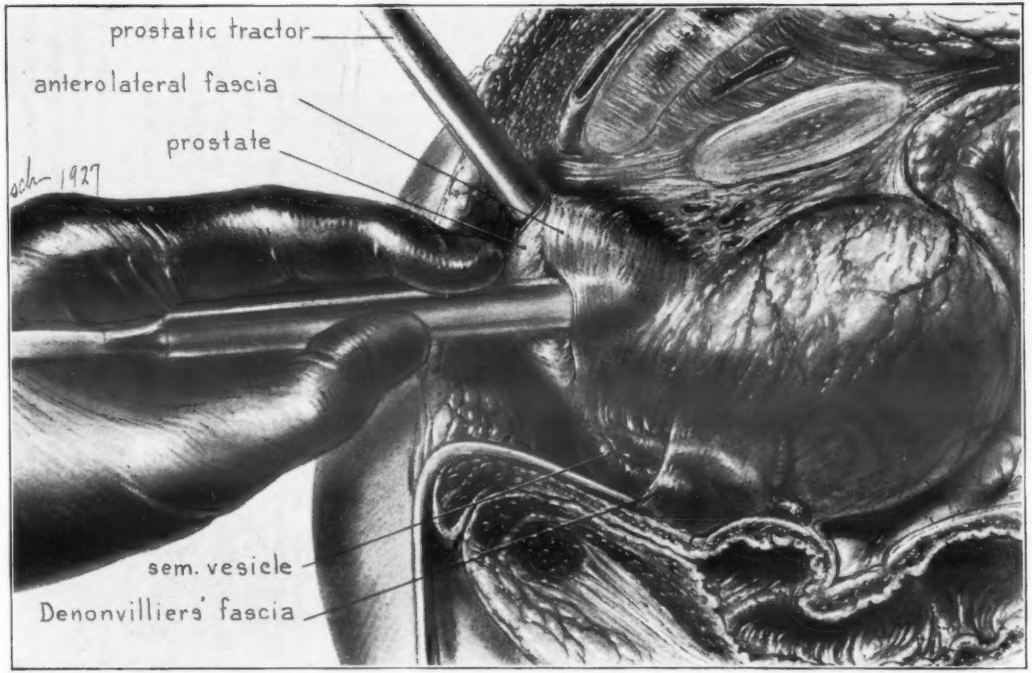


FIG. 15.—Radical operation. Sagittal section showing separation of anterior layer of pelvic fascia from the prostate. This carries with it the great plexus of veins, arteries and nerves which lie behind the pubes.

radical cures obtained by simple removal of the tuberculous epididymis were relatively few, and the ultimate fate of most cases was miserable in the extreme.

It is generally accepted that tuberculous kidney should be operated on as early and as radically as possible, and yet in tuberculosis of the kidney an actively draining escape (the ureter) for the tuberculous process is present. In the case of the seminal vesicles, it is folly to expect the minute ejaculatory ducts to drain the tuberculous process adequately, and a study of our cases showed that the only hope of cure, in the majority of cases, lay in radical surgery.

My first attempt to remove the tuberculous seminal vesicles and a portion of the prostate was done through a suprapubic, retrovesical operation, in which, after stripping the peritoneum from the posterior surface of the bladder, I freed the vesicles and vasa, cut across the upper portions of the prostatic lobes on each side, and

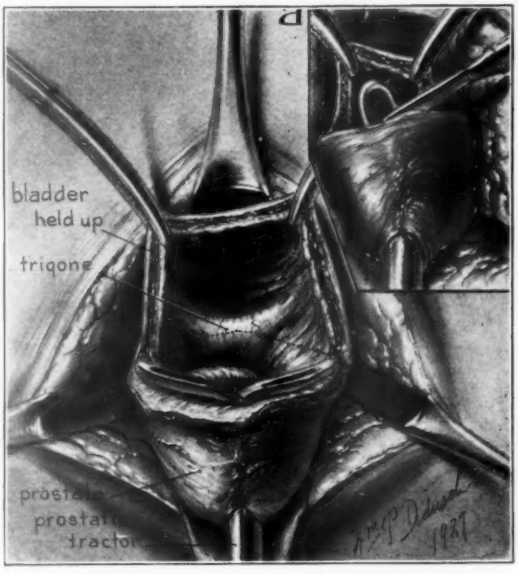


FIG. 16.—Radical operation. (a) Wound in bladder being enlarged on each side with scalpel. Incision runs close to vesicoprostatic juncture. Floor of bladder then exposed; trigone, ureters and median lobe of prostate then seen. Trigone cut across at joint as indicated by dotted line.

removed the mass in one piece, and subsequently through the same incision, removed one or both epididymes, and the remainder of the vasa. The results obtained by this procedure were not satisfactory; miliary tuberculosis resulted from the imperfect uphill drainage.

After experimenting with various types of technique, I finally evolved a method which I have now employed for about twenty years. The prostate and the region of the seminal vesicles are exposed by means of a long tractor in the urethra, and after division of the fascia of Denonvillier, the vesicles and vasa are separated from their attachments, and removed in one piece, with the lateral lobes of the prostate, without injury of the bladder or urethra, which should be kept intact. The tuberculous process in this region is removed completely, except that which may involve the ejaculatory ducts and the thin layer of prostatic tissue, adjacent to the urethra,

but the excellent perineal drainage thus afforded gives this a chance to escape. Through an incision in the groin, the remainder of the involved vas deferens and epididymis is removed. In one-third of my cases it has been necessary to carry out nephrectomy on one side, and regardless of the fact that a large number of the

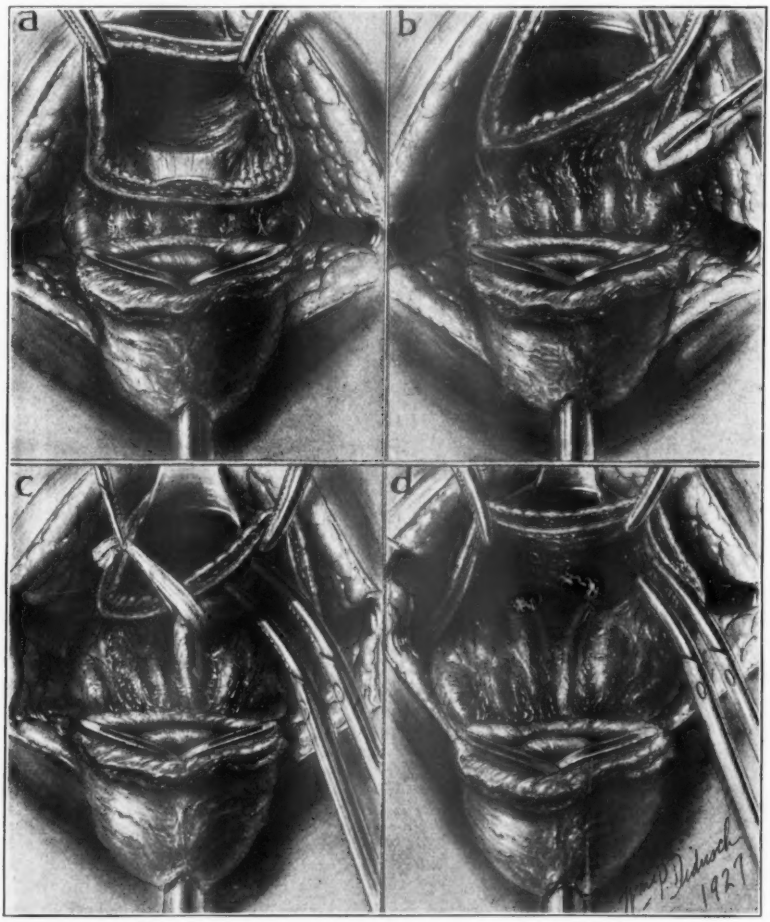


FIG. 17.—Radical operation. Showing the progressive stages in the technique of pushing the bladder and trigone upward and exposing the seminal vesicles and vasa deferentia. (a) The section begun. (b) The vesicles and vasa are exposed by blunt dissection with a Kutner dissector. (c) The left vas deferens is picked up with a tape and doubly clamped as high up as possible, but well below the ureter. (d) Both vasa have been tied, and the pedicle of the left vesicle has been isolated and doubly clamped.

cases have been very extensive in their involvement, a study of the ultimate condition of these cases shows very much better results than we had ever obtained by the incomplete operation of epididymectomy.

One patient was operated on fifteen years ago, being then aged 55. He is now

entirely well. In the case shown, in addition to the tuberculous seminal tract, a tuberculous kidney was also removed. This patient has now been well for nine years. I have not space to give in detail the clinical results obtained by this procedure. They have been published elsewhere [1], but suffice it to say that fourteen

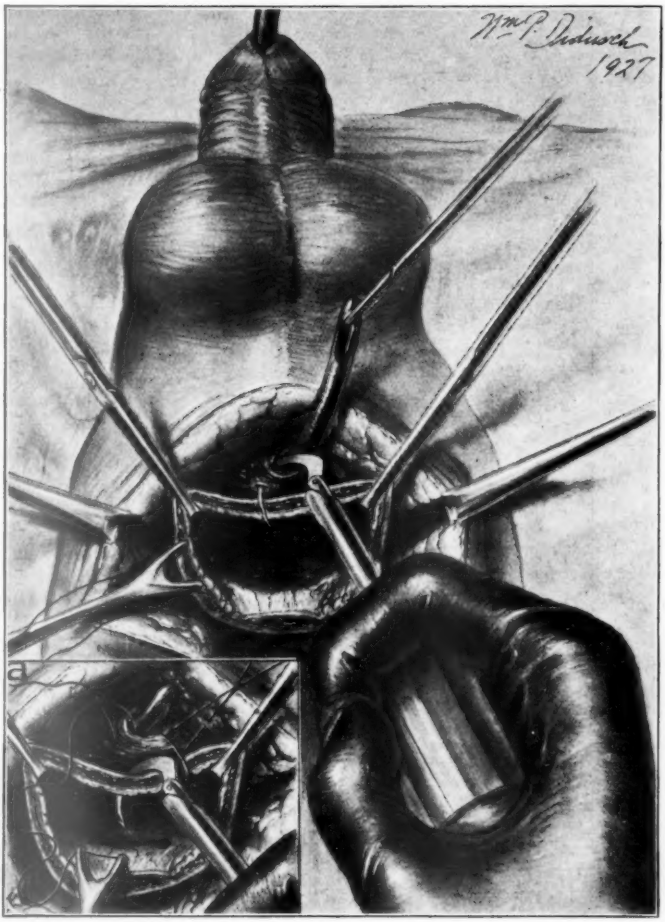


FIG. 18.—Radical operation. With the boomerang needle-holder a chromic catgut suture is drawn through the roof of the stump of the membranous urethra. In (a) the boomerang needle-holder has penetrated the bladder to pull the catgut suture through the bladder wall where it is tied externally.

cases have been followed and found in good condition: over 5 years, nine; 4 years, one; 3 years, three; 1 year after operation, one. I am more than ever convinced that only by this radical operation upon the tuberculous seminal vesicles and lateral lobes of the prostate, is it possible to obtain complete cures of these distressing cases of genito-urinary tuberculosis.

Retention Cysts of the Prostate.—As an additional evidence of the importance of being prepared to carry out perineal surgery, I may mention cysts of the utricle. As shown in fig. 19, on rectal examination, this rounded, fluctuating mass was felt above the prostate between the vesicles. An elevated trigone and catheterization of the utricle and injection with sodium iodide confirmed the diagnosis of a retention cyst. In such cases radical removal is easily carried out without injury to the adjacent seminal tracts.

Diverticulum of the Posterior Urethra.—This is another condition requiring perineal surgery. Here, again, care should be taken to avoid injury of the external sphincter and rectum, by an open operation with good exposure and accurate recognition of the structures encountered. No difficulty has been experienced in removing these cysts and closing the urethral opening.

Rupture of the Posterior Urethra.—Another condition which requires a perineal operation is traumatic rupture of the urethra, with resultant wide separation of the

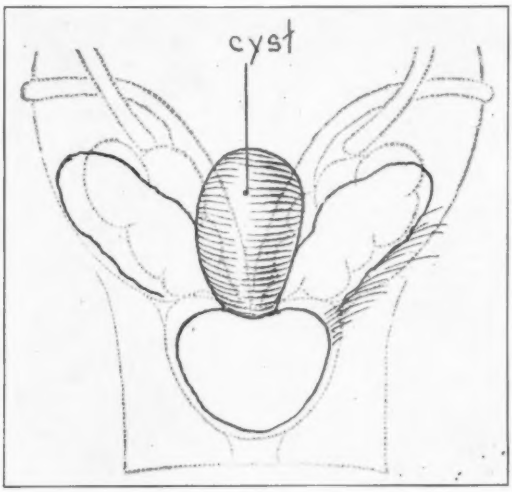


FIG. 19.—Diagram of rectal examination showing cyst of utricle lying between seminal vesicles above prostate.

prostate from the triangular ligament. In such cases the intervening space is often occupied by a large extravasation of blood, and the prostate may be found several inches from the site of the rupture. Through the perineum it is easy to pull the prostate down and suture it to the stump of the torn urethra, and with either a suprapubic or urethral drainage, to obtain a cure without stricture. We do not, however, usually get such cases early. As a rule, they have been treated inadequately by suprapubic drainage, and the space between the prostate and the torn urethra becomes filled with cicatrix. Although difficult, it is quite possible, through a careful open perineal operation, to reach the prostate in its abnormal location, to dissect out the intervening fibrous tissue, see the prostate, reopen its urethra, and anastomose it to the stump of the membranous urethra below. In several cases in which we have carried out this procedure numerous previous attempts to correct the defect had resulted in extensive cicatrices and made the operation difficult, but the results obtained have been uniformly good. In a recent case the rectum had been drawn forward against the symphysis pubis and lay between the

prostate and the stump of the membranous urethra. Extensive dissection to free the rectum was necessary ; the anastomosis was, however, carried out without unusual difficulty.

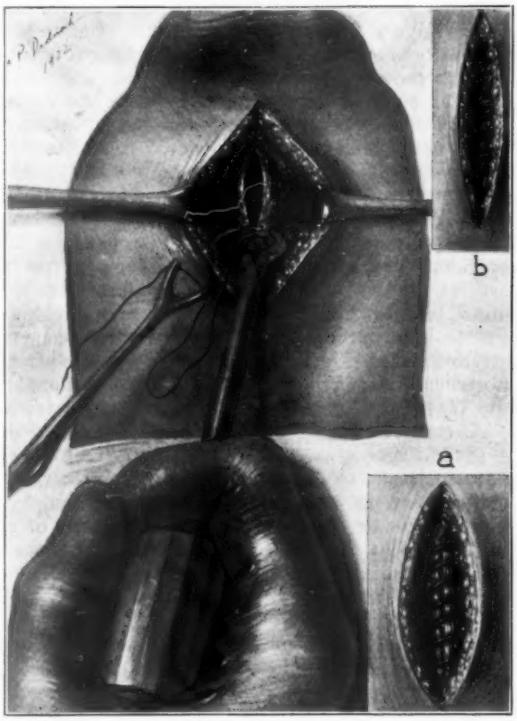


FIG. 20.—Closure of membranous urethra with boomerang needle-holder. Mucous membrane inverted. (a) Approximation of deep perineal muscle around urethra. (b) Closure of superficial muscle and fascia. Skin left open.

Incontinence of Urine.—Another condition, which we can often cure by surgery through the perineum, is post-operative incontinence of urine. Such cases may occur after both perineal and suprapubic prostatectomy, and even after more simple urethral operations, such as urethrotomy for stricture, or contracture of the vesical neck, or even after the punch operation, when the cautery has slipped out and burned the membranous urethra. Since 1911 I have carried out a procedure in which, after supplying suprapubic drainage and resecting and tightening the internal sphincter, I expose the membranous urethra through the perineum—as shown in fig. 20—resect the redundant urethra and scar tissue, and tighten the urethra and muscles in successive layers. In such cases it is necessary to go through the musculature in the region of the triangular ligament surrounding the membranous urethra. Here again it is important to perform a careful open operation, recognizing the tissues, particularly the muscles, as one proceeds, and to obtain proper muscle tissue for approximation in the region of the membranous urethra and internal sphincter. The results obtained by this procedure have been very satisfactory,

particularly after previous perineal operation, when one can follow the scar tissue, and excise it completely. When the operation is required after suprapubic prostatectomy, the absence of scar tissue to direct one to the point of resection makes the operation more difficult and less satisfactory. I believe, however, that with more extensive resection of the urethra and peri-urethral tissues, and tighter closure, the operation can be carried out just as effectively as in the other cases. It is necessary, of course, to produce a stricture, and dilate this afterwards. A very important part of the procedure is the suprapubic drainage, resection and tightening of the internal sphincter, so that urine does not escape and prevent healing of the perineal wound. Keyes' modification of the technique, in which this stage of the operation is omitted, is not, I believe, a step forward.

Recto-urethral Fistula.—This condition, which may follow abscess, or perineal—or suprapubic—prostatectomy can, in my opinion, best be attacked by means of what is usually known as the Young-Stone operation. A circular incision of the anus at the muco-cutaneous juncture, combined with a median perineal incision, affords the proper field of operation. The rectum is separated from within this sphincter, the liberation being carried to a point well above the opening of the urinary fistula, and the tube of intestine drawn down until the fistula-bearing area may be excised completely. After the urethral termination of this stricture has been excised, the opening in the prostatic urethra is closed in two or more layers, the perineum drained, the sphincter repaired, and the rectum approximated to the peri-anal skin, according to the technique of the Whitehead operation. We have now carried out this procedure in 25 cases, with 22 cures. Many of these cases presented extremely difficult surgical problems, several having been operated upon many times, in misguided efforts, by inadequate methods, to close the rectal opening. Only by some radical procedure upon the rectum, in which new tissues are brought down, as above described, is it possible to obtain radical cures in the majority of these severe cases of recto-urethral fistula. This is another reason for an adequate knowledge of the anatomy and technique of perineal exposure.

Impermeable Stricture of the Urethra.—Not infrequently after exposure of the urethra external to severe strictures, it is impossible to find the urethral lumen. If, after a moderate amount of dissection, the opening is not discovered, rather than to continue the extensive dissection it is advisable to expose the membranous urethra behind the stricture, as for perineal prostatectomy, and after carrying out urethrotomy, to pass an instrument retrograde, and thus demonstrate the position of the urethra, so that the operator may accurately excise only the necessary tissues to obtain a cure of the strictured condition. This method, which I presented in 1906, is, I believe, superior both to suprapubic retrograde catheterization, and to the blind Cocke operation, with the retrograde passage of a sound through the perineal wound [2].

Other conditions necessitating perineal surgery behind the triangular ligament might be enumerated, but I hope that those which I have given will suffice to demonstrate the necessity of an adequate anatomical, physiological, and technical knowledge of the perineum and its surgery, and sufficient practice to carry out with facility the various operations which may be so effectively used for the cure of these various conditions.

Before closing, I wish to point out a few important factors in obtaining satisfactory results with a low mortality, in operations upon the region of the prostate. Many of these cases are associated with back-pressure effects, which may go on to extensive impairment—and even to destruction—of the kidneys, and lead to other serious complications. The first prostatic case upon which I operated was that of a man who came to the hospital in uræmic coma. He was given suprapubic drainage, and gradually emerged from his desperate condition; the uræmia disappeared completely, and in a month he was apparently normal. After a pro-

statectomy he made a good convalescence. That was thirty-three years ago, and I realized then, for the first time, the great importance of drainage in prostatic cases with impairment of the kidneys from back-pressure. Subsequently I discovered that if I carried out immediate drainage, either through a catheter or a suprapubic opening, when the bladder had been greatly distended, suppression of urine might occur from the too rapid complete evacuation. Gradual evacuation was then developed, and in order to carry this out more effectively I designed an apparatus by means of which, after determining the pressure under which the bladder was working, it was possible to reduce this pressure gradually, and to bring about adequate complete evacuation of the bladder, without the development of either urinary suppression or hæmorrhage. Whereas, previously, we had lost cases as a result of immediate complete evacuation, we have since had many more desperate cases which have been satisfactorily tided through operation by the use of this method of decompression and evacuation against a gradually reduced pressure. That this method, or some simplification of it, should be employed in many cases, is at once evident.

In such cases, when the bladder cannot be evacuated completely at once, blood chemistry alone can be used to show the condition of the kidneys. Where the renal function is greatly impaired, increase in the blood-urea or non-protein nitrogen, or creatinin, will often be found. In acute cases, however, the blood-chemistry will show a normal condition, although the kidney function may be greatly impaired. As soon as the bladder can be completely emptied by the catheter, it is possible to carry out the phenolsulphonphthalein test, which was introduced in my clinic at the Johns Hopkins Hospital in 1908. For many years we were content to obtain the appearance-time, and the elimination for the first hour and the second hour, but it became evident that such methods were inaccurate, and after a study by one of my house-officers (Shaw) in which the proper curve of phenolsulphonphthalein elimination was worked out by obtaining the estimations at five-minute intervals, it was evident that for satisfactory clinical work, half-hour estimations were necessary. In order to chart these findings, I have recently published a special chart on which are recorded, not only the phenolsulphonphthalein readings, but also the blood-urea, non-protein nitrogen, or creatinin, the urinalyses, blood-pressure, cultures, etc. With these in hand it is easy to chart the phthalein percentage, and also the blood-chemistry, and a beautiful reverse parallelism is found, particularly in these cases of severe back-pressure, with marked impairment of the kidneys and uræmia. The first phenolsulphonphthalein estimation [in a case illustrated by lantern slide during the lecture] showed an appearance-time of thirty minutes (no phthalein) during the first half-hour, 12 to ½ per cent. during the second, 19 per cent. during the third, and 14 per cent. during the fourth half-hours, a total of 46 per cent. within two hours after injection, and 54 per cent. within two hours after appearance of the dye. Chemical examination of the blood, on admission, showed urea 116 mgm. per 100 c.c. With drainage, however, there was a rapid improvement in the renal condition, as shown by the progressively better half-hour phthalein percentages, and a rapid drop in the blood-urea. Such charts give the surgeon a graphic demonstration of the improvement in the patient, and tell him when operation may be satisfactorily carried out. They are also valuable in other types of renal disease, graphically showing the correlated conditions of renal function and blood-chemistry, and the change from day to day.

Infections.—The combating of infections is one of the most difficult tasks in the treatment of prostatic diseases. Almost all operations are accompanied by infection of the wound and of the bladder, and not infrequently there is dissemination to the higher urinary passages—and even the blood-stream—and general septicæmia. The importance of internal antisepsis has been recognized for many years, and there are many valuable drugs, but for the immediate combating of a severe, deep-seated infection, intravenous methods alone offer much assistance. I have been interested

in this problem for many years, and show here a few charts of cases in which severe urinary infections associated with prostatic operations have been combated by intravenous injections of 1 per cent. mercurochrome, in doses varying from 10 to 25 c.c. This

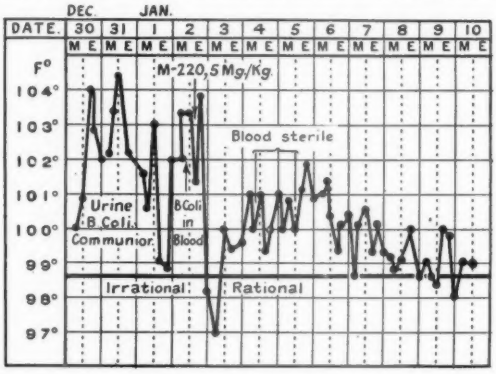


CHART I.—Man, aged 44 years. Double pyelonephritis following ureter catheterization. General septicæmia. *B. coli*. 140 colonies per c.c. blood. Temperature varied from 103° F. to 104° F. On January 3, 1922, patient was irrational. Medical consultants thought the case hopeless, and that patient would not live more than a few hours. Mercurochrome, 1 per cent. 34 c.c., intravenously (5 mg./kg of patient's body weight). Injection was followed by chill, slight rise in temperature and precipitate drop of 6 degrees in about four hours. Blood-culture twelve hours after injection, sterile. Patient had become conscious and was greatly improved. Ate breakfast. Rapid convalescence. Blood-cultures remained sterile. Patient was discharged well in seven days.

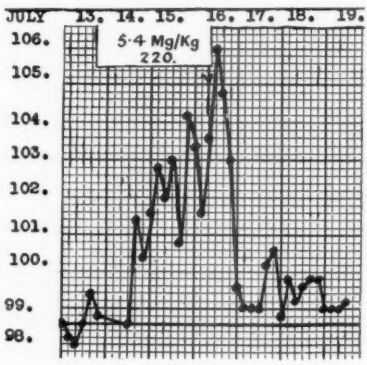


CHART II.

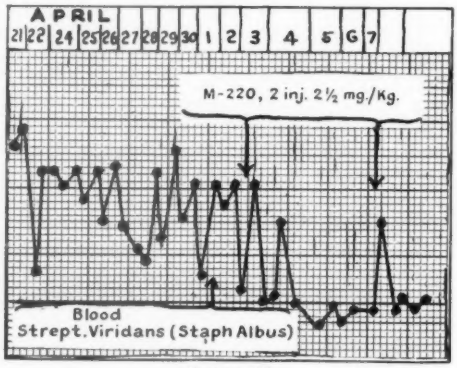


CHART III.

CHART II.—Retroperitoneal abscess following bladder instrumentation. Colon bacillus infection. One injection of 5·4 mgm. per kilogram followed by rapid disappearance of sepsis and recovery without operation.

CHART III.—Female, aged 25. Admitted with infectious nephritis. Acute secondary pyelitis due to *B. coli*, was cleared up under pelvic lavage, but the general condition of the patient became worse, resembling a mild typhoid state. Blood-culture showed *Streptococcus viridans*; white blood-count varied from 9,000 to 37,000. Mercurochrome intravenously, two injections, 2·5 mg./kg., marked improvement following the first injection. Permanent drop in temperature; rapid and uninterrupted recovery after second injection. (Personal communication, Dr. T. Baker, Pittsburg, Pa.)

method, which was first successfully employed in one of my cases in 1923, has now been used in many hundreds of cases in my clinic. A few cases have been chosen to illustrate by charts (Charts II, III, IV, V, VI) the rapid improvement often

obtained. I can definitely state that intravenous mercurochrome may be used in effective doses without fear of injury to the kidneys, intestines or other organs, and that in many cases immediate reactions, accompanied by prompt disappearance

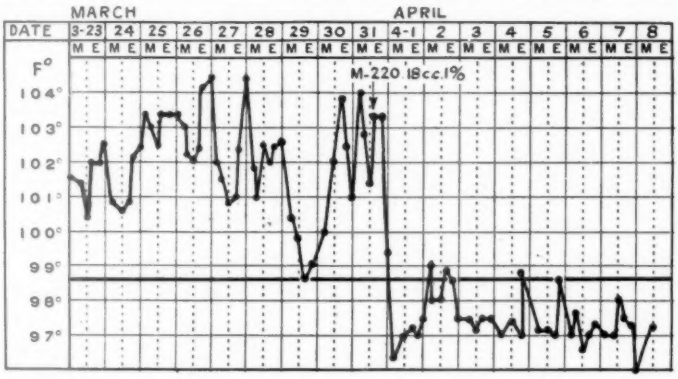


CHART IV.—B.U.I., 13262. Male, aged 61. Admitted to this clinic with diagnosis of benign prostatic hypertrophy. Perineal prostatectomy, after which progress was good until seventeenth day, when septic temperature began, which continued, accompanied by left pyelonephritis for fourteen days, at the end of which time the patient received intravenous mercurochrome, 18 c.c. 1 per cent., followed by chill and drop of temperature to below normal. The sepsis and pyelonephritis were completely terminated, although the urine remained infected.

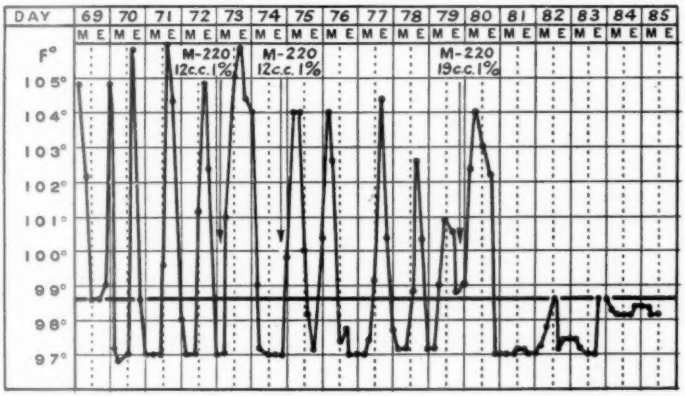


CHART V.—Female, aged 17, admitted University of California Hospital April 10, 1924, with illness of two months' duration, during which there had been chills, fever, skin rash, swollen and painful joints, suppurative gland behind the left ear, cultures from which yielded streptococci. White blood-count, April 24, 20,500. Urine, hyaline casts and *Streptococcus hæmolyticus*. Temperature continued of the septic type indicated until April 23, when the first intravenous injection of mercurochrome, 12 c.c 1 per cent., was given, followed by a second dose, April 29. Following this there was an immediate drop in temperature to below normal. The patient was discharged well in nine days, and continued so under observation. The exact cause of the general infection could not be determined, but the long-continued fever disappeared after the third injection of mercurochrome. (Case of Dr. F. H. Kruse, San Francisco.)

of the septicæmia and sometimes local infections, may be brought about. In *B. staphylococcus* and *B. coli* blood-stream infections, the results have been particularly good. In certain streptococcic septicæmias, failures have been obtained, but in

a long series of septicæmia, cases effective results have been obtained in apparently over 70 per cent. of the cases. In local infections, such as perinephric abscess, and other conditions in the bladder, prostate and urethra, remarkable help has been obtained by intravenous injections of mercurochrome. There have been, of course, numerous failures, but I am so thoroughly imbued with the value of the method that in these cases of prostatic surgery, whenever fever occurs, whether there is a blood infection or not, 10 to 15 c.c. of a 1 per cent. solution of mercurochrome are promptly given intravenously. This is repeated in doses increased by 2 or 3 c.c. each time, and at intervals of two or three days, or oftener, if necessary, until the

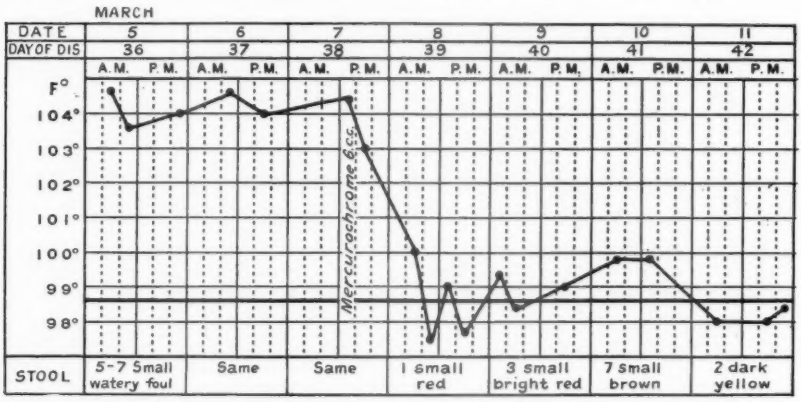


CHART VI.—Girl, aged 5½ years, developed measles followed by broncho-pneumonia and acute otitis media. She had been ill about six weeks, her temperature varying from 102° F. to 105° F. During fourth week of illness she developed severe diarrhœa, four to seven stools daily. Thirty-eighth day of illness, condition desperate; five areas of consolidation in the lungs; temperature 104·6° F. Marked emaciation, both ears discharging profusely, and numerous skin abscesses. Hope of her recovery was abandoned. Intravenous mercurochrome 5 mg./kg., with very little reaction. Temperature fell as if by crisis, and a rapid and uninterrupted recovery began.

septicæmia disappears, or the temperature returns to normal. Where operative intervention—incision and drainage, etc.—is indicated, it is always carried out. Other drugs besides mercurochrome often give excellent results. Intravenous therapy is, I believe, in its infancy and I am certain that there is a brilliant future for it.

My only excuse for the length of this address is a desire to present the variety of surgical experiences responsible for my enthusiasm for the perineal route in operations upon the prostate.

BIBLIOGRAPHY.

[1] YOUNG, H. H., "Brief Note on Ultimate Results of Radical Operation for Tuberculosis of the Seminal Tract," *Journ. Urol.*, 1928, xix, 679-688. [2] "Young's Practice of Urology," Philadelphia, 1926, ii, 578. [3] YOUNG, H. H., and DIDUSCH, W. P., "A Series of Charts for Recording Clinical and Laboratory Examinations in Urologic Cases," *Journ. Urol.*, 1929, xxi, 645-688.

Section of Comparative Medicine.

[*May* 28, 1930.]

Chronic Tracheo-bronchitis of the Dog due to *Oslerus osleri* (Cobbold, 1879).

By Tom Hare.

Chronic tracheo-bronchitis due to *Oslerus osleri* was first described by Osler (1877) in five foxhound puppies, ranging in age from 6 to 8 months, which had died of distemper during an epidemic affecting the Montreal Hunt kennels. Blumberg (1882), at Kasan, received the trachea and lungs of two dogs in which he found the lesion and the parasite. Rabe (1883) described and illustrated the anatomy of the worm found at post-mortem examination in two greyhounds. One of these hounds, affected with the nervous form of distemper, had been recently imported into Germany from England ; the second hound was destroyed on account of a chronic cough. Milks (1916) recorded the clinical history of three cases admitted from the same kennels to the New York State Veterinary College, two of which were destroyed and examined post-mortem. His description is illustrated by three photographs of the parasite and one of the lesions in the trachea and bronchi. Price (1928) found the parasite in the tracheal lesions of a coyote examined post-mortem in Texas. Pillers (1928) described a case in an English fox-terrier ; he also quoted Gaiger as having observed the disease occasionally in foxhounds but never in the pariah dogs of India. Hopkirk (1928) briefly reported a case from New Zealand.

I am indebted to Professor G. H. Wooldridge for the clinical history of the following case :—

Clinical History.—Greyhound bitch, aged about 2 years (at death) ; admitted to the Royal Veterinary College, in October, 1929, with a history of chronic cough of about eight months' duration ; examination revealed enlarged tonsils which were removed surgically. The rasping paroxysmal cough subsided and the bitch was discharged.

The owner reported that the cough returned two weeks after tonsillectomy. The bitch was re-admitted January 25, 1930, with paroxysmal cough and two apparently enlarged tonsils, which were removed two days later. Histologically the excised tissues consisted principally of normal pharyngeal mucosa surrounding tonsillar tissue, the matrix of which was slightly more dense than normal. The bitch died suddenly about twenty-four hours after the second tonsillectomy.

Post-mortem Examination.—Externally no abnormality was found ; the carcase was in good condition. The sites of tonsillectomy were covered with blood-clot, beneath which a thin layer of fibrin had clothed the greater part of each raw surface. The naso-pharynx contained a large amount of blood-clot. A very large quantity of recently swallowed blood was found in the stomach and in the small and large intestines.

The lumen of the trachea and bronchi contained a large amount of clotted blood. On washing away the blood-clots, the mucous membrane of the distal end of the trachea and of the two bronchi and their main branches was found to be studded on all aspects with greyish-white or pink-coloured nodules (fig. 1). These nodules, which varied in size from a pinhead to a small pea, were localized from one inch in front of the bifurcation to their most distal limit of two inches and a quarter along the bronchus supplying the right posterior lobe. The smaller nodules were sessile, the larger were polypoid and compressible, and from a few of these the

pointed ends of delicate nematodes protruded. One worm lay loose on the surface of the mucosa, but it was lost in the washings. Five nodules were counted in front of the bifurcation, twenty-seven in the left bronchus, and thirty-five in the right—a total of sixty-seven. The surrounding mucosa was slightly thickened, opaque and congested.

All lobes of the lungs were sliced along the course of their bronchi, which, together with the bronchioles, were filled with clotted, recently-shed blood. The lungs, especially the anterior lobes, showed a diffuse emphysema of recent formation; there was no chronic emphysema or bronchiectasis.

The blood in the heart and large vessels was fluid, thin, and bright red in colour. The liver and kidneys were paler than normal, apparently as the result of the hæmorrhage. No other macroscopic abnormality was observed.

One of the nodules—the "worm nests" of Osler (1877)—was sent to Mr. A. W.

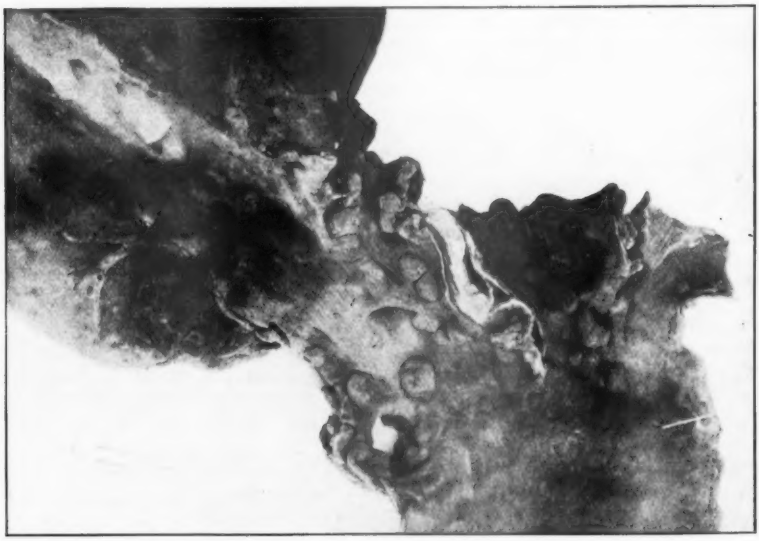


FIG. 1.—Photograph of "worm-nests" in the mucosa of the trachea (at bifurcation) and of the bronchus passing to the right posterior lobe of lung.

Noel Pillers, F.R.C.V.S., who kindly confirmed the identification of the worm as *Oslerus osleri*.

Sections were cut of lung and bronchus, through two pinhead nodules. Histologically, each nodule is a multilocular cystic granuloma, arising in the submucosa, and, by its increase in size, producing pressure atrophy both of the muscularis and surface epithelium of the bronchus. The closely aggregated cysts are occupied by one or more coiled-up *Oslerus osleri* (figs. 2, 3, 4). In each nodule one or more slightly dilated, but otherwise unaltered, bronchial mucous glands lie adjacent to the worm-containing cysts, some of which show a partial lining of flattened epithelium or basement membrane, suggesting that the cystic spaces represent the acini of bronchial mucous glands. The periglandular tissue is infiltrated with fixed connective tissue phagocytes, fibroblasts, lymphocytes, neutrophil leucocytes and an occasional eosinophil leucocyte. Between the nodules the bronchial mucosa is thickened, slightly œdematous and lined by flattened epithelium.

The post-mortem findings suggest that the death of the greyhound was due to asphyxia, associated with profuse hæmorrhage from the sites of tonsillectomy, the blood-vessels of which had been reopened by paroxysmal coughing after recovery from the anæsthetic.

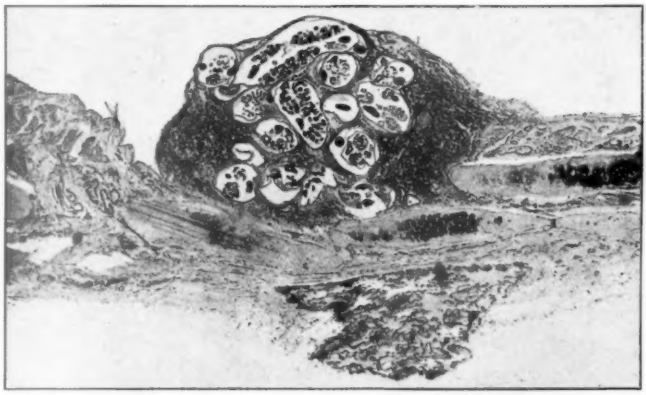


FIG. 2.—Photomicrograph of a "worm-nest" in the mucosa of the left bronchus. × 20.

FIG. 3.—The same, × 50. Note two mucous gland acini in right lower corner.

Discussion.—A review of the recorded cases shows that the disease has a wide geographical distribution. The fifteen canine cases represent a variety of breeds of either sex, of which nine were under two years of age at death; the ages of eight dogs were not recorded (see table). The infection takes a prolonged course, characterized by paroxysms of a dry harsh cough. It does not appear to be fatal, since the affected dogs died from other causes (e.g. distemper) or were destroyed; furthermore

the lesions, from which the nematodes have disappeared, have been described and illustrated by Joest (1924) as chronic hyperplastic tracheitis and by Kitt (1923) as chronic hyperplastic (verrucose or villous) laryngo-tracheitis.

FIG. 4.—The same, × 300. Acinar epithelial cells are destroyed but part of the basement membrane is intact (above and to the left). The lumen is occupied by a female worm, cut in T.S. through the two embryo-containing uteri.

TABLE SUMMARIZING CERTAIN OBSERVATIONS ON 16 CASES OF TRACHEO-BRONCHITIS DUE TO *Oslerus osleri*.

	Author	Animal	Sex	Age at death, in months	Location	Cause of death	Number of "worm-nests"
1	Osler	Foxhound	F.	6—8	Canada	distemper	?
2	,,	,,	M.	6	,,	,,	?
3	,,	,,	M.	6	,,	,,	?
4	,,	,,	F.	7	,,	,,	?
5	,,	,,	M.	8	,,	,,	?
6	Blumberg	Dog	?	?	Russia	?	38
7	,,	,,	?	?	,,	?	4
8	Rabe	Greyhound	M.	12	England	distemper	?
9	,,	,,	M.	?	Germany	destroyed	?
10	Milks	Beagle	F.	?	U.S.A.	,,	30
11	,,	,,	F.	?	,,	,,	6
12	,,	,,	M.	?	,,	(clinical case)	?
13	Price	Coyote	?	?	,,	?	5
14	Pillers	Fox-terrier	F.	18	England	destroyed	20
15	Hopkirk	Collie	F.	?	New Zealand	?	about 24
16	Hare	Greyhound	F.	24	England	operation	67

REFERENCES.

BLUMBERG, C., *Deutsch. Zeitschr. f. Thiermed.*, 1882, viii, 223. HOPKIRK, C. S. M., *Vet. Record*, 1928, viii, 1028. JOEST, E., "Spezielle pathologische Anatomie der Haustiere," Band III, Berlin, 1924. KITT, T., "Lehrbuch der pathologischen Anatomie der Haustiere," Band II. Stuttgart, 1923. MILKS, H. J., *Cornell Veterinarian*, 1916, vi, 50. OSLER, W., *Veterinarian*, 1877, I, 387. PILLERS, A. W. N., *Vet. Record*, 1928, viii, 688. PRICE, E. W., *Journ. of Parasit.*, 1928, xiv, 197. RABE, C., *Deutsch. Zeitschr. f. Thiermed.*, 1883, ix, 180.

ACKNOWLEDGMENT.

I am indebted to Professor R. T. Leiper, F.R.S., for guidance in interpreting the histological appearances of the nematode and for drawing my attention to a further publication—Vogel, H., "Ueber die Nematodengattung *Oslerus* Hall 1921, und zwei neue Arten derselben: *Oslerus cynopitheci* und *Oslerus felis*." *Centralbl f. Bakt.* etc. I Abt. Orig., 1928, cix, 430.

Section of Odontology.

[*June* 2, 1930.]

A Complex Composite Odontome.

By GERALD HARBOROW, L.D.S., and J. G. TURNER, F.R.C.S., L.D.S.

I.—Mr. Gerald Harborow.

THE history of this case is very similar to that of all odontomes, especially those of this type. The patient, a male aged 19, came to the Dental Department of the Metropolitan Hospital for relief of pain, which he thought was caused by an abscess in the left lower molar region. This pain had been very severe for three or four days; it came on suddenly and kept him awake at night. Before this attack he had no indication of any abnormal condition, and he had never had a tooth extracted. He noticed, however, that his face was now slightly swollen on that side. The swelling was slight, but distinct.

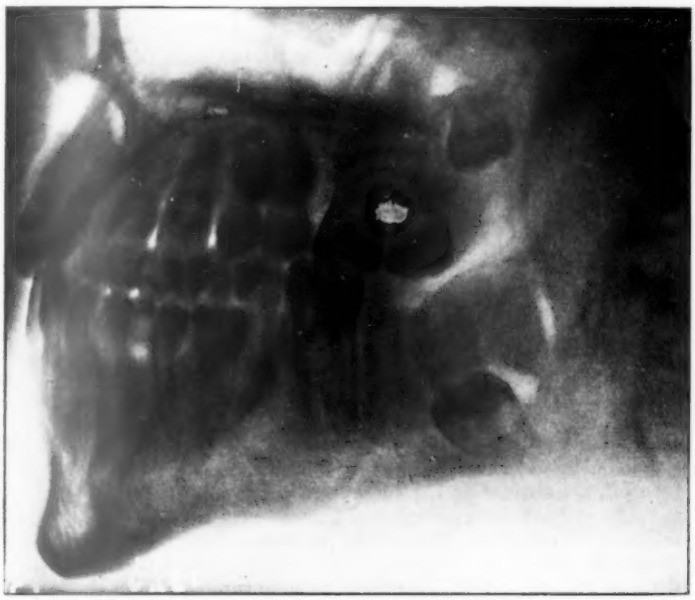


FIG. 1.—Radiograph showing position of odontome with the third molar lying below on the border of the mandible.

On examination I found the second and third left molars absent and a hard swelling extending immediately behind the first molar, occupying the space normally taken by the second and third molars and encroaching into the sulcus. The lingual surface appeared normal. There was little tenderness when I saw him and the pain had diminished considerably. There was a small sinus over the alveolar ridge, and pressure on this spot caused a small quantity of pus to exude. Exploring this sinus with a probe, I came on what I thought to be a root. There was only a very thin covering of gum over this surface. I had the patient examined by X-rays, and the result showed a mass of growth occupying the second molar region.

Under this, in the centre, was a tooth deep down on the lower border of the mandible. This I took to be the third molar, the mass taking the place of the second molar, which was absent (fig. 1).

The radiologist's report is as follows : "$\overline{7}$ is missing, $\overline{8}$ is lying very low in the ramus, its roots are bent round at the lower border. Bone above it is very dense and there is a suggestion of a large sequestrum."

I had the patient taken into a ward and operated on him under ether and chloroform anæsthesia. I made an incision over the whole extent of the swelling and removed the gum overlying the upper surface. I then used a curved elevator at the anterior border of the growth, immediately behind the first molar, and with very little difficulty the odontome moved. At first I thought the jaw had fractured, but when I again used the elevator the mass came out whole, together with its capsule. Further examination proved the jaw to be undamaged. The cavity was quite smooth. I thought it wise to leave the molar which was under the odontome. There was very little hæmorrhage and there was no need to pack the cavity. The only after-treatment that was necessary was constant irrigation by syringing with mild antiseptics.

The specimen measures $1\frac{1}{4}$ in. in length and $\frac{3}{4}$ in. both in width and depth.

This odontome falls into the class of complex composite odontomes, under the nomenclature adopted by the Committee appointed by the British Dental Association, in their "Report on Odontomes." Their definition is as follows : "Complex composite odontomes are those composite odontomes, the tissues of which are irregularly intermingled and which have no definite shape."

The number of reported cases of these odontomes in the list given in "The Report on Odontomes" is twenty-five; of these, sixteen were in the lower molar region, and one was in the lower premolar region. The eight cases reported in which the odontome was in the maxilla, were more widely varied in their position. One was definitely in the canine region, one was in the canine and premolar region and five were in the molar region. The remaining one was in the premolar region. It seems, therefore, that the mandibular molar region is a common site for these odontomes, the left and right sides being equally common.

II.—Mr. J. G. Turner (*Histological Report from the Research Laboratory, Royal Dental Hospital of London*).

The mass is enclosed in loosely adherent fibrous tissue, but when the soft covering has been torn off, the surface of the tumour is rough and mammillated. The same rough surface is exposed on opening the fibrous coat in any part of the tumour. A piece of the solid body was broken off in extraction and the exposed surface shows a columnar structure. X-rays show a solid mass. Sections were prepared from the surrounding soft tissues and from the solid tumour ; from the latter both by grinding and by decalcification. Ground sections show that the columnar appearance alluded to above is due to the presence of more or less parallel calcified papillæ of dentine coated with enamel, 1 mm. or so in diameter. To these papillæ the rough surface of the tumour is due. The illustration (fig. 2) shows that the papillæ are branched. In a neighbouring part the papillæ are smaller and less regular, and the microscope suggests tubes or columns of enamel in a bed of dentine. Deeper in the body of the tumour dentine alone is found, and the figure shows well the point at which enamel ceases abruptly. Cementum is not to be found. The suggestion of cementum in the illustration is due to interglobular spaces.

The decalcified sections, taken transversely through the papillary part, show a general groundwork of dentine broken by numerous spaces of widely varying sizes and shapes. Where the spaces are empty they indicate dissolved enamel. Some

of the smaller and regular spaces are filled with horny epithelium or decalcified enamel suggesting solid columns, but perhaps only indicating the level at which the calcified papilla was cut. A few are filled with the branched connective-tissue cells of pulp-tissue, and it is easy to identify these spaces by the fact that the surrounding dentine tubules are large and crowded. Most of the spaces contain both decalcified enamel and epithelial structures which are recognizable as derived from an enamel organ. The illustration (fig. 3, p. 52) shows one of the larger spaces in which the epithelial nature of many of the cells is readily recognizable, the rest of the tissue being composed of a delicate connective tissue much infiltrated by

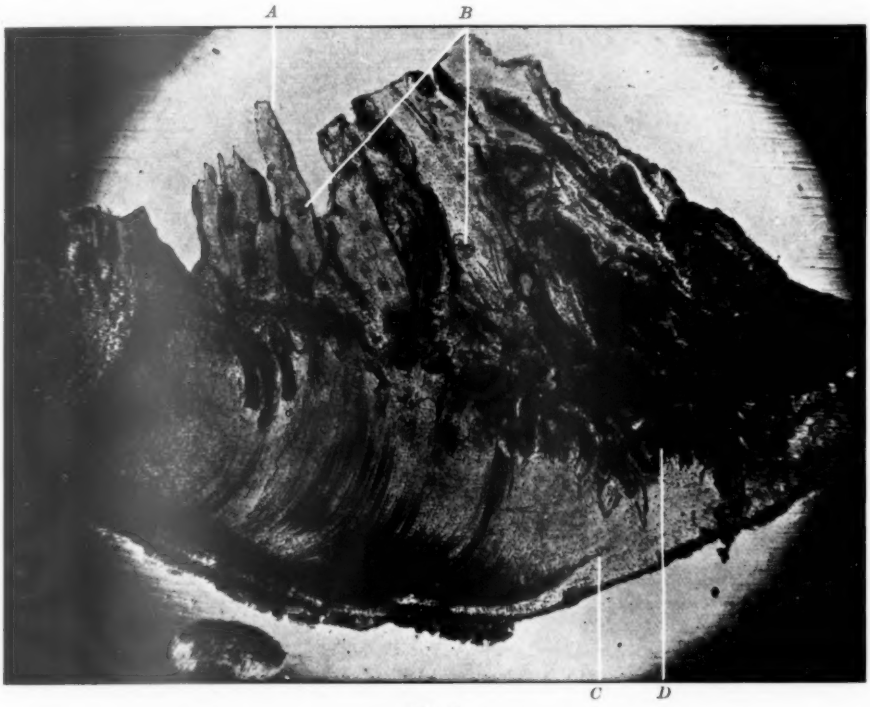


FIG. 2.

A, Calcified papillæ. *B*, Sections of branches of papillæ.
C, Dentine. *D*, Limit of calcified papillæ.

inflammatory exudation and showing many blood-vessels. In parts the epithelial surface of this tissue is horny and stains deeply with eosin (fig. 4, p. 53).

The other epithelial structure derived from the enamel-organ consists of horny epithelium already mentioned staining deeply with hæmatoxylin (indicating that it was partly calcified). This substance is widely diffused through the section and fills in small spaces and crevices, and is also found in the larger spaces, and in contiguity with decalcified enamel. It represents an abortive attempt at enamel formation. It is also found in isolated masses in the fibrous tissue surrounding the

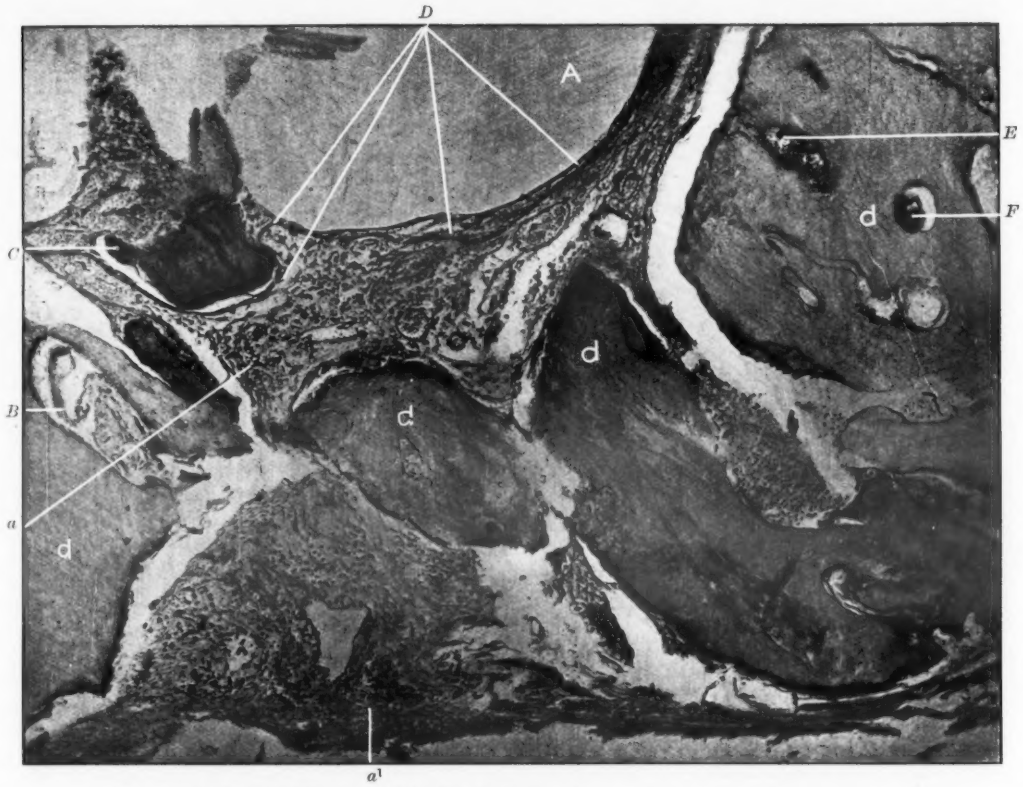


FIG. 3.—*A*, Space left by completely dissolved enamel.
a = delicate connective tissue carrying enamel-organ epithelium and continuous through a1, with a similar structure spreading over the surface of the hard mass.

B, Decalcified enamel. *F and C*, Horny epithelium staining deeply with hæmatoxylin.
D, Enamel-organ epithelium. *d*, Dentine. *E*, Pulp tissue.

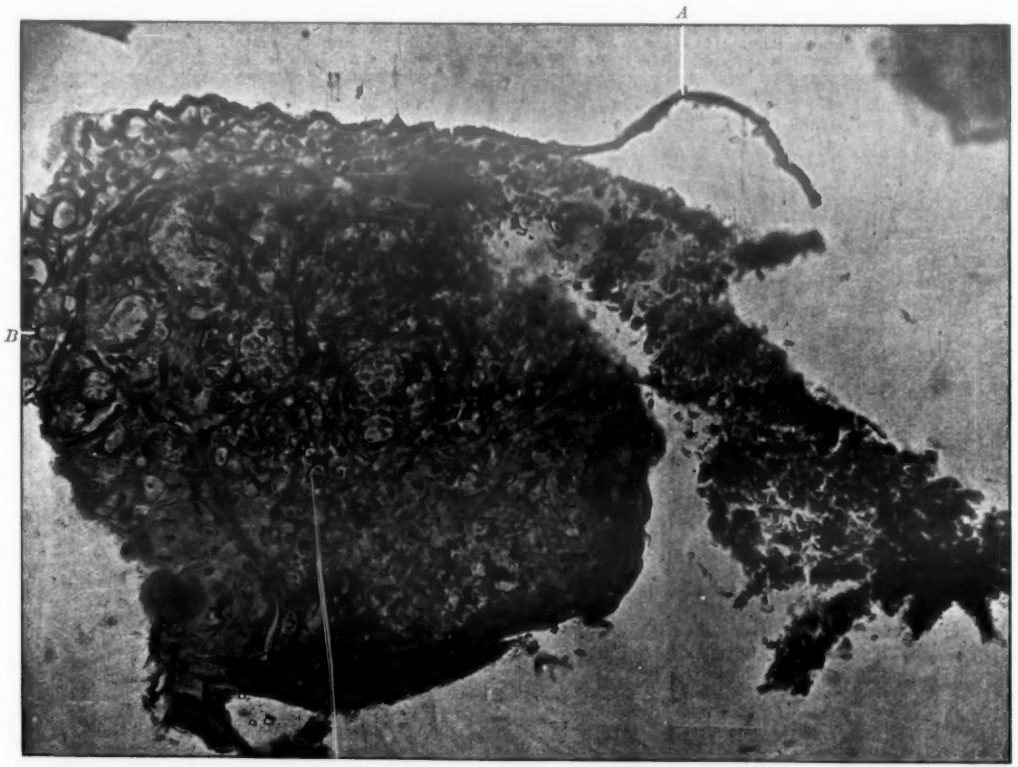


FIG. 4.—*A*, Horny epithelium taking the eosin stain well. *B*, Soft tissue containing epithelium and showing inflammatory infiltration.

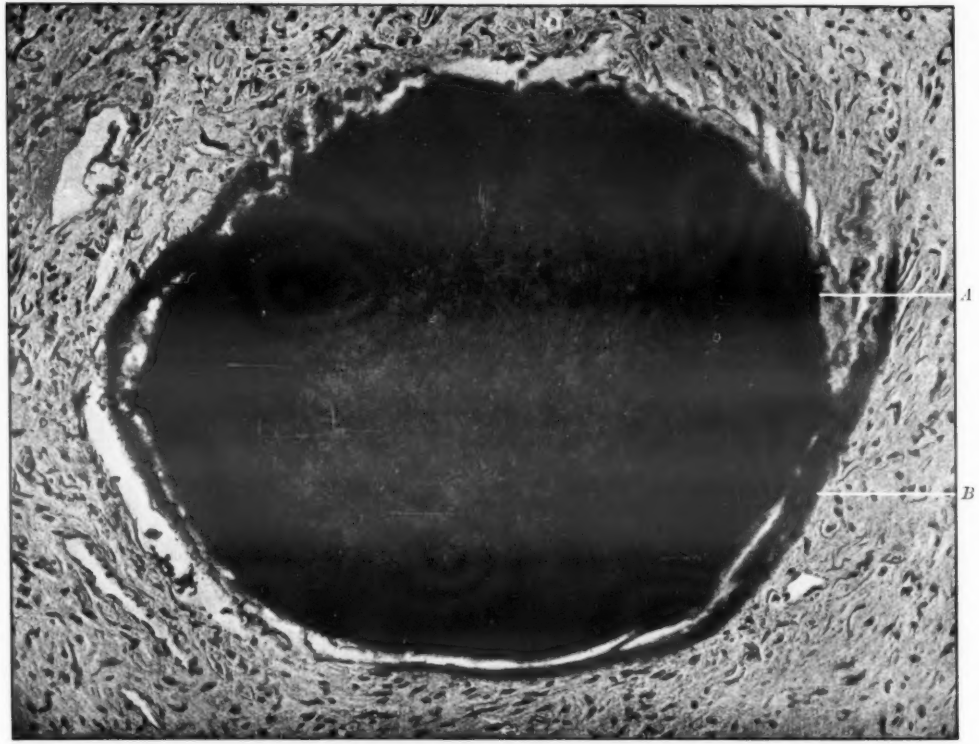


FIG. 5.—*A*, Horny epithelium. *B*, Living epithelium. Mass of horny epithelium staining deeply with hæmatoxylin, with surrounding living epithelium ; from the connective-tissue capsule.

tumour. It suggests a far more intimate mingling of enamel and dentine than do the more striking calcified papillæ first described. The adjacent dentine is often almost amorphous, but in some parts can be identified as peripheral dentine by the small size and branching of the tubules.

Sections of the surrounding soft tissues show that it consists of fibrous tissue in which are found little epithelial masses, some of which have formed epithelial pearls (fig. 5). Sections of the soft tissue immediately overlying the hard tissues show that the enamel-organ tissue above alluded to spreads over the surface of the hard tissues. Sections of both hard and soft tissues from the opposite pole of the tumour (i.e., the radicular part) show similar pictures, and fig. 6 shows well the epithelial lining of the fibrous coat and its outgrowths.

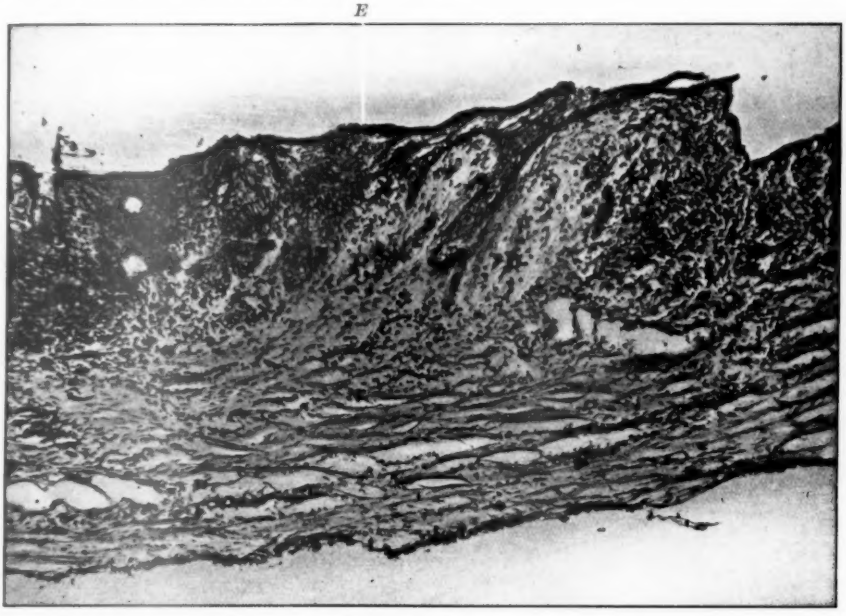


FIG. 6.—*E*, Epithelial lining of the capsule of the tumour. This epithelium faced the solid mass, and recalls the epithelial lining of a normal tooth-crypt or of a dentigerous cyst.

If we recall the histology of a multilocular epithelial cystic tumour (in which cysts are often very inconspicuous) it will be seen that calcification of such a tumour would produce just such a solid mass as I have described. In one of my cases the tumour took the form of a pedicled papilloma, and projected into a cyst cavity. In another direction the epithelial findings in the surrounding soft parts link the tumour up with the tooth-nests not infrequently found in the premaxillary region. In a case which I have described in the *Royal Dental Hospital Reports*,[1] I found in the fibrous tissue in which the various teeth and denticles of these tooth-nests are embedded, solid epithelial masses, epithelial tubes having a gland-like structure, and epithelial masses showing abortive attempts at enamel formation, exactly like those found in the present tumour. Fig. 6 shows also an important point of resemblance to a normal tooth-crypt and to a dentigerous cyst.

[1] *Royal Dental Hospital of London Annual Reports*, 1924, p. 118.

The question has been raised as to when the tumour ceases to grow. The evidence of the outliers of epithelium seems to me to show that the soft parts of the tumour increase by peripheral spread of epithelium (determining perhaps the later formation of dentine) so long as there is a connective-tissue bed to grow in, and that when a surface is reached, the whole process is brought to an end by infection, but some dependence on the normal calcification age of teeth is probable as regards the solid parts. The case shows the importance of preserving and examining the soft tissues surrounding solid odontomes, a point to which Pickerill has also drawn

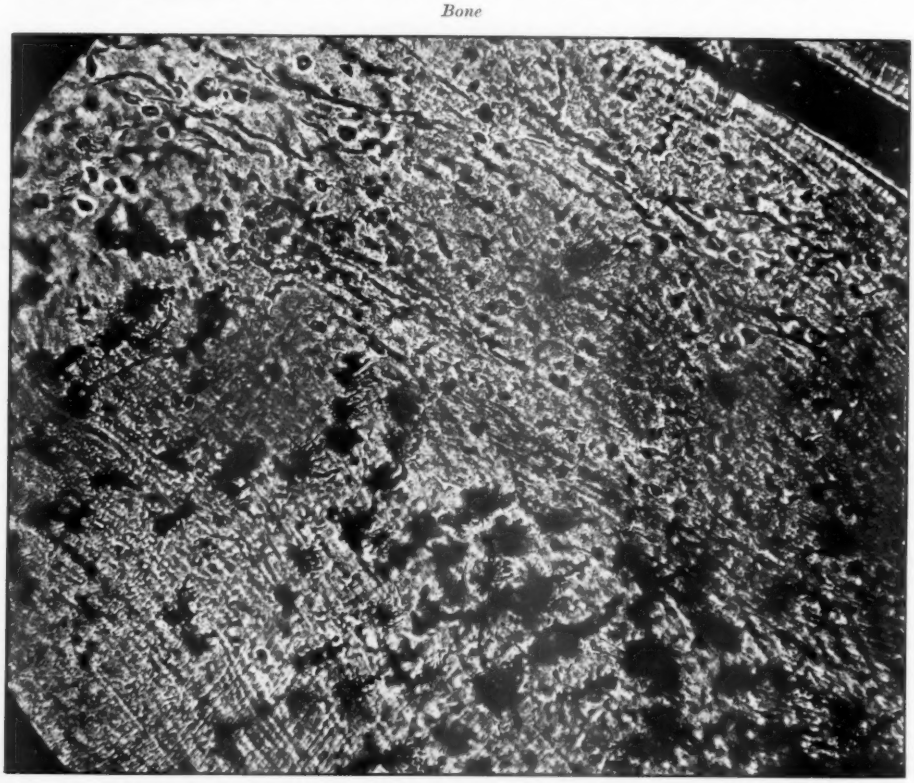


FIG. 7.—Ground section showing cementum and bone with no visible line of demarcation. (Mr. A. E. Carden's case.)

attention and which Mr. Harborow had in mind when he at once put this specimen in formalin. I think it very likely that the soft parts will provide a better basis for classification than the hard parts.

Mr. A. E. Carden's Case of Odontome.—A second specimen was sent me by Mr. Carden, of Cheltenham. The clinical history was one of long-standing inflammatory trouble of the mandible, resulting in a general overgrowth of the horizontal part. X-ray examination showed more than one centre of trouble. The clinical symptoms were those of necrosis—suppuration and general illness. Two or three masses of hard tooth-like nature were removed at different times, there being no difficulty in

taking them away. The mass which I have is about $1\frac{1}{2}$ in. × $\frac{3}{4}$ in. × $\frac{3}{4}$ in. at its largest part. Its surface is rough, but not eroded. On attempting to cut it, it was found extremely hard and a full section was impossible. However, I laid it open and found it to consist of an exostosed root partly surrounded by a mass of dense bone, that is to say, only the cement surface is embraced by the bone, not the surface that represents the connection with the tooth-crown. There is extensive exostosis of the cementum, recognizable by the large branched lacunæ (fig. 7). Outside the cement, and in parts separated from it by a cleft which may have contained soft tissue, but in other parts, as far as I can judge, directly continuous with it, is a mass of very dense bone, recognized by its small unbranched lacunæ and by blood-vessels. The mass is obviously of inflammatory origin, the dead root being a source of low-grade infection, which eventually was of sufficient intensity to destroy the blood supply of the sclerosed bone. But the point of interest is: what is the origin of the dense bone? Cement or jaw-bone? In trying to elucidate this point I have examined similar specimens, one met with by Mr. H. Stobie and one by Mr. F. N. Holborn. Both had the same clinical history—one denoting inflammatory origin from infected roots, and both ended in suppuration with easy removal, but in neither case is it possible to point to a line marking bone off from cementum. The bone is not, perhaps, so dense as in Mr. Carden's case.

Mr. H. A. Edmunds gave me a tooth which is of considerable interest in this connection. It was an upper canine, pulp alive, but perhaps slightly affected by pyorrhœa. On the side of the root, towards the apex, was a white knob. On making a section I found it to consist of hard bone filling in an area of absorption in the exostosed cementum of the tooth. The new bone closely fills in the absorbed area, and no dividing line can be recognized. Still it seems probable that this new bone was jaw-bone and that it came away with the tooth because it so closely interdigitated with the absorbed cementum.

It is worth noting that I cannot find on any of the specimens examined any microscopic evidence of the absorption of the surface—perhaps because the surface has been ground away in preparing the sections.

Discussion.—Mr. EVELYN SPRAWSON said that he gathered that Mr. Harborow and Mr. Turner were describing this odontome as if it were a calcified multilocular cyst. He did not think it was so, particularly as a tooth was absent from the normal series. No evidence had yet been produced that multilocular cysts had anything to do with the dental formative organs, except that they occurred in the mouth; moreover, multilocular cysts were not infrequently found when the whole of the permanent teeth were *in situ*, and they had never been described as containing any calcified dental tissue. It was obvious that multilocular cysts must be derived from epithelium in the mouth, but he thought it probable that they had no relation to the tooth-forming epithelium. They nearly always occurred in the same portion of the jaw. If a portion of a multilocular cyst was removed and sent to a pathological laboratory without indicating its site, it would be regarded as a basal-celled carcinoma (as the rodent ulcer is also named), and indeed there were strong histological similarities between these cysts and rodent ulcers. Moreover, the histological appearances of multilocular cysts were almost, if not quite, identical with those of the epithelial tumours which occasionally occurred in the anterior portion of the pituitary body, the epithelium of which had its origin from an extension of the epithelium lining the mouth. Basal-celled carcinomata (rodent ulcers) were also similar to multilocular cysts in that they also had their favourite sites, but occasionally varied them. He thought that in the past the histological similarities between the cells of multilocular cysts and enamel organs had been much overstated.

Mr. G. B. PRITCHARD said that the association of deposits of bone with the roots of teeth, without intervening soft tissue was probably more common than might be imagined, and the cases were nearly always of a chronic inflammatory nature. In a few specimens with which he had dealt there were indications of a definite thickening of the tooth. In those cases in which the deposit of bone occurred on the outside there was invariably evidence of chronic

inflammation. In spite of the closest examination, it was exceedingly difficult to say if there had been any absorption of the cementum. With regard to the bone deposit, the histological characteristics were closely allied to what was considered normal bone.

Mr. J. G. TURNER said he agreed with Mr. Sprawson that multilocular cystic tumours were found with all the teeth *in situ* and embedded or sitting over a third molar or with the third molar sitting over the tumour. They appeared to be fairly common in the lower jaw as well as in the upper jaw. The point he desired to make was that the facts of the solid tumour were brought into line with those of a soft tumour of epithelial origin. Here was a case that looked as if it were an aberration of the normal organ. In other cases there was a soft tissue without any calcification. Both soft and hard tissue formation might be expected at any point from the time of the first sequestration. Therefore there seemed to be no difficulty in imagining that a similar tumour could be produced at any time. With regard to Mr. Pritchard's observations, inostosis into dentine was always easily marked off. The inostosis into cement in Mr. Edmunds' case was well marked. Granuloma that calcified or ossified would give very irregular bone and capillary blood-vessels.

[After the meeting Sir Frank Colyer gave a demonstration on the specimens in the Odontological Museum.]

Section of Tropical Diseases and Parasitology.

[*May* 1, 1930.]

A Little-known Type of Chronic Colitis.

By ALDO CASTELLANI, K.C.M.G. (HON.), D.S.C., M.D., F.R.C.P.

(*Director of Tropical Medicine, Ross Institute for Tropical Diseases, London*).

IN this paper I propose to call attention once more to a type of chronic colitis which, although in my experience quite common in the tropics as well as in the temperate zone, is very little known. This colitis is due to a group of bacilli which I have called the "meta-dysentery bacilli." This is not the place in which to give a description of these organisms: I have described them in several previous papers. It suffices to state that they are similar to the true dysentery bacilli (Dysentery-para-dysentery: Shiga-Kruse, Flexner, Hiss-Russell) in that they produce no gas in any sugar, but differ from them in producing acidity in lactose, and in coagulating milk. The production of acidity in lactose and the coagulation of milk may be exceedingly slow and may not take place before the fifteenth day of incubation at from 35° to 37° C. There are several varieties of these bacilli; the following two chief types may be separated: (1) *ceylonensis* A type. (2) *ceylonensis* B type.

The organisms of the *ceylonensis* A type produce acidity in lactose slowly—at times extremely slowly—and the acidity is often in very small amount; coagulation of milk is very slow, indol is often negative. The bacilli of the *ceylonensis* B type produce acidity in lactose rapidly, and the coagulation of milk is usually fairly rapid.

The principal species of bacilli belonging to the meta-dysentery group are the following:

(1) *Bacillus coli-anaerogenes* of Lembke. In 1896 Lembke isolated from the excreta of dogs a coliform bacillus producing acid, but not gas, in glucose and lactose media, which he called *B. coli-anaerogenes*. Nabarro at one time was inclined to identify with it all the meta-dysentery bacilli. In an interesting paper published in the *Journal of Pathology* (I. B. 1923, v. 26, p. 429) he says:

> "Lembke, in 1896, isolated from the excreta of dogs a coliform bacillus producing acid but not gas in glucose and lactose media, to which he gave the name *B. coli-anaerogenes*. Between 1905 and 1912 Castellani isolated several varieties in Ceylon, which he has named *B. ceylonensis*, *B. madampensis*, *B. bentotensis*. These organisms all agree in the property of fermenting sugars, etc., with the formation of acid alone, the difference between them being of a minor nature."

Nabarro further states that he first isolated *B. coli-anaerogenes* in 1912 from a case of dysentery at the Wakefield Asylum.

(2) *Bacillus pyogenes fœtidus* (Passet 1902).—This bacillus is motile. It was found in cases of abscesses without apparent intestinal symptoms.

(3) *Bacillus ceylonensis* A.—This was first isolated by me in Ceylon in 1905, and described in 1906 and 1907. The recent investigation by Cerruti has shown that the so-called "Sonne's bacillus," on which numerous papers have been published in

recent years, is serologically identical with it; as is also *B. pseudo-dysenteriæ* E of Kruse.

(4) *Bacillus ceylonensis* B.—This was isolated by me in Ceylon in 1905.

(5) *Bacillus meta-dysentericus.*—This was isolated by me in Ceylon in 1904, but was not named for some years.

(6) *Bacillus madampensis.*—Isolated by me in 1910, and described in 1911.

(7) *Bacillus bentotensis.*—Described by me in Ceylon in 1912.

(8) *Bacillus gintottensis.*—Described by me in 1910.

(9) Certain bacilli found by Duval in America in infantile diarrhœa seem to me to belong to the meta-dysentery group and not to the para-dysentery or Flexner groups.

(10) One of the pseudo-dysenteric bacilli, described by Kruse long ago, *pseudo-dysentericus* strain E, belongs to the meta-dysentery group, as it ferments lactose (acidity only).

(11) Sonne's bacillus, on which a number of papers have been published recently, belongs to the meta-dysentery group. Cerruti considers it to be identical with *B. ceylonensis* A.

The principal meta-dysentery bacilli are collected in the table (p. 41).

Cerruti has recently grouped all the meta-dysentery bacilli into one genus (Castellanus) and, as adhering strictly to the rules of nomenclature, some of the old terms used by me cannot stand, he has created new specific names. The principal species is C. *castellanii* (= B. *ceylonensis* B). Of this species he distinguishes several varieties, the principal ones being C. *castellanii* var. *krusecastellanii* (= B. *ceylonensis* A) and C. *castellanii* var. *metadysentericus* (= B. *meta-dysentericus*).

Geographical Distribution.—The condition seems to be a cosmopolitan one. It is found in the tropics and the subtropics, but is also very common in many parts of the temperate zones. In Europe I have seen cases contracted in Italy, France, Spain, the Balkans, and even in this country. It appears to be particularly frequent in Italy and Spain.

Symptomatology.—The type of chronic colitis to which I am calling attention is characterized by recurrent attacks of simple diarrhœa with absence, or only occasional presence, of dysenteric symptoms. The stools during the attack are fluid, brownish or yellow, at times frothy; as a rule they do not contain muco-pus or blood, but there are exceptions. Each attack may begin suddenly with severe abdominal pain, or only abdominal discomfort may be felt; the attack lasts from a few hours to several days. In the intervals between the attacks—and these intervals may be prolonged, lasting for many months—the patient may feel fairly well, but as a rule complains of occasional slight abdominal discomfort and flatulency; he often feels run down, tired, nervous and not inclined for work. These cases go on for years, a little better, a little worse: the patients consult many practitioners, and are generally told that they are suffering from "colitis" or "intestinal subinfection"; sometimes the diagnosis "mucous colitis" and "abdominal neurasthenia" is made. Not rarely, atypical appendicitis is suspected and an operation is performed. In other cases cholecystitis is suspected and the gall-bladder is removed. Palpation of the abdomen reveals very little; occasionally there is some slight tenderness and resistance, especially in the sigmoid region. The patients try all kinds of treatment, Plombières douching being probably the most popular, and next to that, streptococcal vaccines and various so-called intestinal disinfectants. The result is generally unsatisfactory. Some of these patients have a wretched life and are a burden to themselves and their families.

Frequency.—In my experience the type of chronic colitis I have described is quite common. Of the cases of chronic colitis without evident dysenteric symptoms, investigated during the last three years, a very large number were due to the meta-dysentery bacilli. Out of sixty cases of thoroughly investigated chronic, clinically

TABLE SHOWING BIOCHEMICAL CHARACTERS OF CERTAIN BACILLI OF THE META-DYSENTERY GROUP.

(Reactions after an incubation period of three weeks at 37° C.)

	Motility	Gram	Gelatine	Serum	Litmus milk	Lactose	Glucose	Levulose	Maltose	Galactose	Mannitol	Dulcitol	Saccharose	Inulin	Isodulcitol	Inositol	Adonitol	Arabinose	Amygdalin	Salicin	Sorbitol	Raffinose	Dextrin	Erythrite	Glycerine	Potato starch	Indol	Lead agar
B. ceylonensis A, Castellani 1907 (strain PD)	O	O	O	O	AC	O or AVS	A	A	A	A	A	O	A	O	A	O	O	A	O	O	O	A	AS	A	A	O	O	O
B. ceylonensis B, Castellani, 1907 (strain RR)	O	O	O	O	AC	A	A	A	A	A	A	A	O or A	O	A	O	O	A	O	O	A	A	A	O	A	O or A	+	O
B. meta-dysentericus Castellani Var. A (strain 2)	O	O	O	O	AC	A	A	A	A	A	O or A	O	A	O	A	O	O	A	O	O	O	A	O	O	O	O	+ O	
B. madampensis Castellani 1911 (strain H)	O	O	O	O	AC	A	A	A	A	A	A	O	AS	O	A	O	O	A	O	O	AVS	A	A	O	A	O	+	O
B. pyogenes fœtidus Passet 1902	+	O	O	O	AC	A	A	A	A	A	A	A	A	—	—	—	—	A	—	—	—	A	A	—	—	—	+	—
B. bentotensis Castellani	+	O	O	O	A or A-Alk	A	A	A	A	A	O	AS	A	O	O	A	O	O	O	O or AS	O	O or AS	O	O	A	—	+	
B. bentotensoides Castellani	+	O	O	O	AC	A	A	A	A	A	O	A	A	O	O	A	O	O	O	O or AS	O	O or AS	O or AS	O	A	—	OA O +	—

O = negative, viz., absence of clotting of milk, absence of acidity and gas in sugar media (the medium may become alkaline).
+ = positive, viz., presence of clotting of milk, presence of acid and gas in sugar media, etc. A = acid.
AC = acid and clot. Alk = alkaline. — = reaction unknown. AS = acid slightly.
AVS = acid very slightly.

non-dysenteric colitis, in which amœbiasis could be excluded by the absence of cysts, fifty gave a positive agglutination in a dilution of 1 in 80 and over, for one or more varieties of meta-dysentery bacilli, and in nineteen the bacilli were isolated from the stools. In ten cases there was no agglutination, and no meta-dysentery bacilli could be found; in one, a variety of *Bacillus asiaticus* was found; in two, a variety of *Bacillus asiatoideus* highly agglutinated by the patient's blood; in two others no causative agent could be found.

Diagnosis.—The diagnosis is difficult; the bacteriological examination of the stools may be negative many times before meta-dysentery organisms are found. In the chronic cases the procedure that I have found most helpful is testing the blood for agglutination for the principal varieties of the group. My routine method is to test the blood of every suspicious case for agglutination for *B. ceylonensis* B, *B. ceylonensis* A, and *B. meta-dysentericus*. When the agglutination is higher than 1 in 80, repeated bacteriological examinations of the stools will as a rule reveal, sooner or later, the presence of meta-dysentery organisms, although, as I have already stated, many examinations may have to be carried out before a successful one is obtained. The stool for examination must be absolutely fresh. The colonies on MacConkey's agar plates are delicate and after a day or two may have a pinkish or reddish colour.

Differential Diagnosis.—A very similar chronic, clinical syndrome may be found caused by *E. histolytica*; very rarely, if ever, by bacilli of the true dysenteric group (Shiga-Kruse, Flexner, and Hiss-Russell, or dysentery-para-dysentery group). Only repeated and thorough microscopical and bacteriological examinations will enable one to make a differential diagnosis.

Prognosis.—If the correct diagnosis is not made, the prognosis is bad, although not with regard to life. There is no natural tendency to cure, and the condition in many cases goes on indefinitely, although there may be prolonged periods of great improvement and even apparent cure.

Treatment.—The treatment is difficult. It is almost impossible to cure these cases if they do not enter a hospital or nursing home. I insist on complete rest in bed and usually a fluid diet: in this country milk is usually well tolerated and in most cases a milk diet is best. In the tropics or subtropics milk is seldom tolerated, and then a diet, consisting of albumen water, chicken broth, panopeptone, peptonoids has to be recommended. It is advisable always to begin the treatment with a dose of castor oil. In a few cases so-called intestinal disinfectants, such as salol, are useful, but what is most useful, in my experience, is the administration of a meta-dysentery vaccine, autogenous if possible, though I have had good case-results by using a stock meta-dysentery vaccine, containing the principal varieties of the meta-dysentery bacilli, viz., *ceylonensis* A and B, and *B. meta-dysentericus*. The treatment should last on the average six weeks, and, after an interval of from two to four months, it should be repeated, even if the symptoms of colitis have disappeared.

Before concluding I should like to call attention to the desirability of investigating certain forms of colitis, which are known by local names, and about which very little is known. I may mention as an example "Gyppy Tommy." Anybody who has been in Egypt knows the term which, of course, like every other popular term, is applied to many different conditions, but principally to a type of intestinal dyspepsia, with abdominal discomfort and occasional attacks of diarrhœa, seldom if ever being dysenteric. During the last two years three patients have come to consult me after a prolonged residence in Egypt, suffering from what they called "Gyppy Tommy." The bacteriological examinations proved them to be suffering from the colitis I have described, due to meta-dysentery bacilli.

BIBLIOGRAPHY.

CASTELLANI, *Ceylon Medical Reports and Bulletin*, Ceylon Branch, British Medical Association, 1906. "Cases of Fever Confounded with Typhoid," *Journ. of Hyg.*, 1907, vii, 1. Reports of the Advisory Committee for the Tropical Diseases Research Fund, 1911. Observations on Some Intestinal Bacteria found in Man, *Centralblatt f. Bakt.*, 1912, xiv, 262. "Infezioni tifiche, Paratifiche e miste della zona Adriatico-Balcanica," *Ann. di Med. Nav. e Col.*, 1916, ii, 453. "Alcune osservazioni sulla etiologia, diagnosi e cura della dissenteria," *ibid.*, 1918, i, 52. "Reports of the Inter-Allied Sanitary Commission," Office International d'Hygiène Publique, 1918-19. CASTELLANI and CHALMERS, A. J., "Chapters on Classification of Bacteria," "Manual of Tropical Medicine," London, 1919. CASTELLANI, "Classification de certains groupes de bacilles aërobies de l'intestin humain," *Ann. de Inst. Pasteur*, 1920, ix, 600. "Classification of Bacterial Dysenteries and of Dysentery Bacilli," *Amer. Journ. Trop. Med.*, 1927, vii, 199. "Observations on a Little-known Group of Anaerogenic Intestinal Bacteria," *Proc. Roy. Soc. Med.*, 1927, xx (Sect. Path., 21), 1261. "Meta-dysentery," *Lancet*, 1929 (ii), 370. "Meta-dysentery," *Ann. Intern. Med.*, vol. II, No. 2, 1928. CERRUTI, C. F., "Bacilli meta-dissenterici (Castellani) e B. coli-anaërogenes (Lembke), *Annali di Medicina Navale e Coloniale*, Anno XXXIV (Anno VI), Vol. II, Fasc. III-8, 1928. FICHERA, G., "Dissenteria da B. ceylonensis, *Policlinico* (sez. prat.), 1929, xxxvi, 550. NABARRO, D., *Journ. Path. and Bact.*, 1923, xxvi, 429. OLIVI, G., "The Virulence of Bacillus Meta-dysentericus (Castellani) in the Rabbit," *Journ. Trop. Med. and Hyg.*, 1923, xxiv, 123.

Discussion.—Major-General D. HARVEY said there were two points on which he would like some information. Many of these cases of chronic diarrhœa had begun some years ago in the tropics. Could Sir Aldo say what was the actual causal agent in the initial stage? Were these meta-dysentery bacilli capable of producing an acute attack of dysenteric diarrhœa; might they not be present in an intestine damaged by a previous attack of specific dysentery?

The other point was with regard to the agglutination; Sir Aldo relied on an agglutination titre of 1/80 as diagnostic; this would certainly not be accepted as diagnostic with the Flexner group; were not the meta-dysentery bacilli also agglutinated to that titre by some normal sera?

Dr. M. WEINBREN said that the subject of Sir Aldo's paper might appear to be a long way removed from his (the speaker's) work, yet they touched each other at the point of diagnosis.

Sir Aldo had said that in some of the chronic cases the appendix and the gall-bladder had been removed without benefit. He (Dr. Weinbren) was convinced that the reason why the gall-bladder and appendix were suspected was that reflex irritation of the duodenum had been produced by the inflammatory changes in the colon.

Sir ALDO CASTELLANI: In reply to Major-General Harvey, I may state that the meta-dysentery bacilli are capable of producing an acute attack of dysentery.

I agree with Dr. Weinbren with regard to the reflex action he has mentioned.

Bilharzia Disease in Children.

By J. B. CHRISTOPHERSON, C.B.E., M.D., F.R.C.P. (President).

THE first point which I wish to make is that bilharzia is notably a children's disease, and as evidence of this fact, I am showing a series of photographs taken in various countries where the disease is endemic.

It is a common sight in Egypt to see children naked, playing in the infected irrigation channels which run through the village. Children cannot fail to contract bilharzia disease under such conditions (fig. 1, p. 44).

Again, Captain Dye's photographs show native children in Central Africa, immersed in the bilharzia-infected, reed-choked pools of Nyasaland.

The next picture shows a Central African child with the enlarged spleen and liver of *Schistosoma mansoni*; and the next, also a photograph of Captain Dye's, a child with *Schistosoma mansoni* in the act of infecting the snails in Nyasaland. Children are the chief disseminators of the disease in Africa (figs. 2 and 3).

FIG. 1.—A typical Egyptian village (El Marg). Children playing in an irrigation stream which is infested with *Bullinus contortus*, *Planorbis boissyi* and other intermediary hosts of Schistosoma.—Photograph supplied by Dr. R. B. Coleman and Dr. J. Bateman.

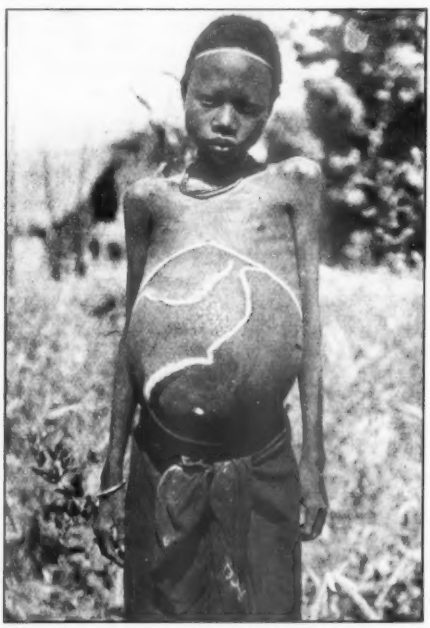


FIG. 2.—Native child, one of twenty similar cases in the same district discovered by Dr. H. S. Stannus in Nyasaland in 1914, north of Lake Nyasa, near Karonga. Dr. Dye afterwards established the diagnosis of Schistosomiasis mansoni.—Photograph by Dr. H. S. Stannus.

Again, in South Africa, Dr. Cawston's photograph shows "children catching bilharzia in Natal."

FIG. 3.—Children are the chief reservoirs of human schistosomiasis and the most important disseminators of the disease in Africa.—Photograph by Dr. W. H. Dye.

FIG. 4.—Chinese child with Schistosomiasis japonica. Enlarged liver and spleen, stunted growth.—Photograph by Dr. E. Carroll Faust (Exhibit in British Empire Exhibition, 1924).

Finally, Dr. Faust's photograph from China tells the same tale: bilharziasis—a children's disease. It also shows how it affects growth and physical development in children (fig. 4).

I have no doubt that photographs from the West Indies, the other notable centre of bilharzia endemicity, would show that the children are the prime sufferers and disseminators of bilharzia disease there.

It may be asked, if it is a children's disease why has so little been written about bilharziasis in children?

In Egypt, whence come most of the clinical, pathological, and biological facts of bilharziasis, the great majority of cases which the doctors see are in adults, the most aggravated cases are in adults; children suffering from bilharziasis form the least numerous class of persons in the hospitals.[1]

The serious surgical complications of bilharziasis occur in adults: Cystitis, stricture, perineal fistula, bilharzial tumours and papillomata; bilharzial masses of granulation tissue in bladder and bowel; stone, pyelitis, pyelonephritis, uræmia, and cancer. Bilharziasis in its most serious clinical aspects is certainly a disease of adults.

Nevertheless these disastrous and terrible complications so common in adult Egyptians are the result of disease of many years' standing, they are mostly the terminal picture of constant re-infection over a long period of time, originating in childhood.

Bilharzia worms are potentially long-lived.[2] Persons living in endemic localities, exposed to constant cumulative reinfections, harbour in their portal systems literally hundreds of worms. The early stages of the disease are painless and often pass unnoticed.

Before the introduction of the antimony tartrate treatment, the disease was looked on as incurable; hæmaturia with a little pain passed unheeded, and children with bilharziasis were not brought to the doctor.

Kautsky, quoted by Sandwith,[3] examined 124 apparently healthy school children in Cairo and found that 78% had bilharzia ova in the urine.

More recently Khalil systematically examined the children of the village of Kom-Ombo in Upper Egypt and found living ova in 80%. Again at Saft-el-Enab,[4] a village of lower Egypt, 375 persons were examined by Khalil, of whom 56 were children between the ages of 1 and 10 years—77·6% of the latter were passing bilharzia ova in urine or fæces, or both. Therefore I think I am justified in drawing attention to the fact that bilharziasis is a children's disease.

The bilharzia parasite lives in the blood, derives its food from the blood, discards its waste products into the blood; it causes anæmia and its attendant evils and there can be little doubt that the physical and moral development of many a child in Egypt is embarrassed by bilharzia disease.

Now the schools offer the best organization for dealing with the bilharzia problem in children. It is easy in schools to collect the cases and control them during treatment. A great number of carriers and disseminators of the disease can thus be effectively dealt with. The schools also offer the best medium for teaching the biology and the implicated hygienic and sanitary principles, for the children to carry home and disseminate among their relations. But it is with the individual child that I shall deal in this paper.

The Age when Infection is Acquired.—Bilharziasis is not a congenital disease. It is acquired only when skin or mucous membrane comes in contact with infected water. Egyptian children contract bilharziasis from the irrigation canals and

1 The children were, until recently, not brought for medical treatment.

2 Christopherson records a case in which bilharziasis was contracted in Nyasaland; the patient passed living ova for twenty-eight years, although reinfection was impossible by residence in England.

3 Sandwith "Medical Diseases of Egypt."

4 Population of Saft-el-Enab 5,929—of whom 375 persons were examined: 73% had *S. hæmatobium* and 34·7% *S. mansoni*; fifty-six were children between 1 and 10 years of age.

puddles of the village, as soon as they can toddle about.[5] Cases of bilharzia-infected infants, attracted by the prospect of cure, now come to the notice of the doctor more frequently than formerly.

Antimony tartrate is still the established remedy of choice for bilharziasis. In 1928, 400,000 cases were treated by antimony tartrate in the Egyptian Government bilharzia annexes. This figure does not include patients treated in the Government Hospital with no special bilharzia annexe, or in other hospitals, such as the large Church Missionary Society Hospital in Cairo, nor does it include the patients treated privately.

But in spite of the fact that about three quarters of a million cases are treated in Egypt yearly by antimony tartrate, this figure—large as it is—is not sufficiently large to make an obvious impression on bilharziasis as a national disease, and it appears to me probable that bilharziasis will not be eradicated from Egypt until the children in the village schools are systematically treated, for they are the chief carriers and disseminators of the disease. Therefore treatment of the children is of supreme importance.[6]

Two cases of bilharziasis in English children—a girl aged 10, and a boy aged 14—treated by me with antimony tartrate, with disappointing effects, are the basis of this communication. Both contracted the disease in South Africa. Other cases of English children whom I have treated with antimony have been completely satisfactory, but the fact that these two took the antimony badly, contrary to the general experience that children tolerate antimony well, is sufficient reason for considering why they were intolerant. The girl had lived all her life in the Transvaal; she contracted the disease in 1922, six months before I saw her, by bathing at Silvertown, near Pretoria. The bilharzia was discovered by the doctor who was attending her for enteric fever.[7] In January, 1923, at Pretoria, she was given a course of antimony tartrate injections twice weekly, commencing with gr. $\frac{1}{4}$, and proceeding with gr. $\frac{1}{2}$, gr. $\frac{3}{4}$, gr. 1, gr. $1\frac{1}{4}$, gr. $1\frac{3}{4}$. (Total 5 or $5\frac{1}{2}$ gr.) After the sixth dose (gr. $1\frac{3}{4}$) she had a rigor, the temperature mounting to 105° F, and the injections were suspended. When she came to England some months later, she was palish, had frequency of micturition, enuresis and hæmaturia. Thinking that the first reaction was probably due to the fact that she was convalescing after enteric fever, and that gr. $1\frac{3}{4}$ had been too large a dose, I recommended another course of antimony. On June 5, 1923, the second course of sod. ant. tartrate was commenced with gr. $\frac{1}{2}$, increasing the dose by gr. $\frac{1}{4}$, given on alternate days until the third injection, gr. 1, was reached on the fourth day. Two days later gr. 1 was repeated, then gr. 1 on two consecutive days. On the second of these days she had some frequency of micturition, but appeared to take the injection well, and the following day I gave her gr. $1\frac{1}{2}$; she coughed and later became a little pale and clammy, and vomited when she reached home. Next day the cystitis was better, and I gave her gr. 1. She took it well, and there was no cough. Two days later I gave her gr. $1\frac{1}{4}$; she appeared to take it well, but half an hour later she was pale, clammy, and collapsed; her lips were blue and her pupils dilated, and she complained of pain in the thighs and temples. She was given hot water bottles, warm diluted brandy by mouth, and strychnine hypodermically,

5 Sandwith, "Medical Diseases of Egypt," 1905, says it is unknown in infants, commencing about 4 years of age; but H. B. Day, *Lancet*, 1921 (i), 525, in his series of 1,000 cases treated with antimony tartrate, mentioned cases of $2\frac{1}{2}$ years old.

6 I do not hold that treatment of children is by itself sufficient to eradicate bilharziasis from a country I agree with the medical authorities of Egypt, who advised in 1924, in addition to the treatment of individual cases: (i) Protection of the irrigation canals against pollution. (ii) Guarding water used for household purposes against contamination. (iii) Extermination of molluscs—intermediary hosts—by drying up the small irrigation canals in rotation and treating the small pools left by copper sulphate. *Vide* Ankylostomiasis and Bilharziasis in Egypt, *Report and Notes of the Public Health Laboratories*, 1924. Also Khalil, *Lancet*, 1927 (ii), 1235.

7 Although the enteric fever and the bilharziasis were concurrent, the course of the bilharziasis appeared to be unmodified.—J. B. C.

her extremities were rubbed, and she was well enough to go home in three hours. Such symptoms, however, are alarming. This patient, aged 10, and weighing 6 st., had, in all, gr. 8 for the second course, scarcely sufficient to kill off all the parasites. It appeared to me that once allergic symptoms had been produced, she became intolerant, sensitized, as it were, to antimony, and a smaller dose, gr. $1\frac{1}{4}$, reproduced allergic symptoms, although she had taken gr. $1\frac{1}{2}$ quite well during the previous course in Africa.

My second case occurred as recently as Christmas, 1929. A delicate-looking public schoolboy, aged 14, was suffering from hæmaturia, and bilharzia ova were found in his urine. The disease had been contracted in South Africa, 200 miles from Johannesburg, in 1927.[8] The boy also had had malaria in South Africa—the last attack two years previous to the time I saw him. He was a fragile little boy, weighing $7\frac{1}{2}$ st., and had been in England since August, 1928.

I had some difficulty in this case in finding veins for injection. I gave gr. $\frac{1}{4}$, gr. $\frac{1}{2}$, gr. $\frac{5}{8}$ on three consecutive days, and then a little local phlebitis occurred and he had five days' rest, injections being resumed on December 26 with gr. $\frac{1}{2}$. On December 28 I gave $\frac{7}{10}$, on December 30 gr. $\frac{9}{10}$, on January 1, 1930, gr. 1, two days later gr. 1, two days after this gr. $1\frac{1}{4}$, two days later, January 7, gr. $\frac{3}{4}$, in all approximately gr. $7\frac{1}{4}$—ten injections in twenty-one days. He had some allergic symptoms after the gr. $1\frac{1}{4}$ dose—headache, pallor wiry pulse, and a feeling of sickness—so I reduced the dose and gave gr. $\frac{3}{4}$. After a two days' interval, the allergic symptoms recurred and I abandoned the injections on January 7. The bilharzia symptoms disappeared with the gr. $7\frac{1}{4}$, and the urine was clear, acid, 1020, no albumin, and contained no ova—in fact, it was quite normal and remained so for six weeks, until February 23, when microscopic blood was noticed in the urine, and the following week live ova reappeared. In this case, as in that of the girl and in other cases it appeared to me that when once allergic symptoms had been aroused, the patient became as it were sensitized to antimony, and intolerant even of the smaller dose of gr. $\frac{3}{4}$, although he had previously taken gr. $1\frac{1}{4}$ well.

We do not come across many children in London with bilharzia disease, but those I have met with have all been British. In my experience English children are not so tolerant of antimony tartrate as African children. In the Egyptian Sudan where the people are of Arab, negroid, or mixed descent, children take antimony remarkably well; beyond coughing and sometimes vomiting, they show no symptoms of intolerance. This is also the case with the Egyptian children in J. G. Bateman's practice at the C.M.S Hospital in Cairo.

In South Africa, J. G. Cawston states that children suffering from bilharziasis vary considerably in their tolerance of antimony; he points out that probably this is due to the fact that various races (Dutch, Afrikander, Negro, Indian, half-castes), and various diets are met with.

This point, concerning the various susceptibilities of children of different nationalities has not so far received due notice. If it be true, what is the reason? Cawston[9] notes that Indian children have little tendency to vomit after a dose of antimony tartrate, and that although many of his Indian patients were so young that he might have hesitated to give the full dose, yet experience showed that Indian children take antimony well. He ascribes this toleration to the vegetarian diet[10] of the Indians. Egyptian children also take antimony well (as do Sudanese and African children), and it appears a credible conclusion that the tolerance of native

8 Contracted in 1927. Noticed nine months after bathing in the White River (Wilge River), a branch of the Vaal in the O.F.S. Four out of six boys who bathed in all about ten times contracted bilharziasis.

9 *Journ. of Trop. Med. and Hyg.*, 1930, xxxiii, 7.

10 Cawston also alludes to the taking of alcohol as the cause of patients not taking antimony well. This may be so for habitual alcoholics.

children is due to the fact that their diet is largely carbohydrate and vegetable. It may be that European children do not tolerate antimony tartrate so well as African children because European diet is largely protein. Now, the digestion and elaboration of protein food is one of the principal functions of the liver; anything which interferes with the metabolism of the liver cell affects protein digestion.

I have not sufficient facts whereon to base a dogmatic statement, but, assuming that antimony is a hepatic toxin, the symptoms of antimony intolerance appear to be those of interference with the protein metabolism of the liver.

Now, adult patients who drink alcohol take antimony badly; they are more subject than others to the intolerable muscular pains which are the bugbear in bilharzia treatment in Europeans. Whether an alcoholic parent begets children who are intolerant of antimony, I will not attempt to answer, but in both the cases of intolerance to antimony which I have just described there was an alcoholic history in one parent.

Let me take it for granted for the moment that antimony (like arsenic and phosphorus, members of the same chemical group as antimony, having the same chemical and biochemical relationships) is a hepatic toxin, interfering with the metabolism of the liver cell. The allergic symptoms produced by antimony administration for bilharziasis remind one of shock-like collapse or allergic symptoms, described by Dale,[11] characteristic of histamine introduced into the circulation in experimental animals, and it would seem possible that the allergic or collapse-like symptoms which sometimes accompany antimony administration—alarming to the doctor, for they may end in death—are due to the production of a histamine-like body in the liver, through interference with protein metabolism, a toxic histamine-like body formed in lieu of the harmless end-product of protein digestion, which is carried under normal circumstances to the muscles as food.

Allergic symptoms are, I think, more frequent in children than in adults, but there appears to be a corresponding symptom of irregular hepatic metabolism, which occurs frequently in adults, and which I do not remember at all in children. When the larger doses of antimony tartrate are being approached, adult patients complain sometimes of excruciating muscular pain coming on the night of the injection. Added to the pain is a more or less complete state of temporary paralysis—a patient so affected cannot move the limbs, or turn over, or get out of bed. The symptoms pass off and are not attended by any serious result, but they may induce the patient not to return for completion of the course of treatment. Now, this complication also may be the result of interference by the antimony with the protein metabolism of the liver cell, a by-product being turned out which, carried in the circulation to the muscles, causes pain because it is not the food which the muscles are needing, but a toxin which they should not have.

It is almost universally taught that contra-indications against antimony administration are cardiac disease and renal disease.[12] Hepatic disease is entirely omitted in this connection from the textbooks.

It is true that on general grounds one would hesitate to give antimony tartrate in cardiac and renal cases, but there is no evidence that antimony tartrate, in the therapeutic doses prescribed in bilharziasis, affects the cardiac muscle or the renal epithelium. On the contrary, Noque and Boulay, in 1923,[13] treated with antimony fifteen cases of bilharziasis with definite chronic nephritis with œdema; all bore the treatment well. But little is found in bilharzia literature about hepatic disease and

11 H. H. Dale, Croonian Lecture, 1928, before the Royal College of Physicians.

12 I omit debility, acute febrile conditions, concurrent diseases, including other helminthic infections. No one will dispute that these should be dealt with before antimony is given.—J. B. C.

13 Noque and Boulay, "Preliminary Note on Renal Insufficiency in cases of Bilharzia Patients. Tartar Emetic Treatment," *Bull. Soc. Path. Exot.*, xvi, 564.

hepatic insufficiency being a contra-indication to antimony treatment in bilharziasis.[14]

Briefly, the following are the grounds for considering that antimony tartrate is a hepatic toxin :—

(1) Antimony belongs to the same chemical group as arsenic and phosphorus, both of which are hepatic toxins. Similar chemical reactions imply similar (though not necessarily the same) biochemical relations.

(2) Experimental evidence with rabbits shows that when antimony tartrate is given in lethal doses most damage is seen in the liver cells.[15]

(3) Jaundice and bilious vomiting, two cardinal hepatic symptoms, occur in a certain number of cases treated with antimony tartrate.[16]

(4) Treatment by antimony tartrate is contra-indicated when there is cirrhosis of the liver with ascites in Schistosomiasis mansoni.

(5) Cases of Schistosomiasis japonica, with marked cirrhosis of the liver and ascites, do not do well under antimony treatment.[17]

(6) Finally, symptoms of shock and allergy in children and the intense muscular pains in adults can best be explained by assuming interference with hepatic protein metabolism, the formation of a "histamine-like" body or the formation of a toxin due to incomplete protein metabolism.

Whilst discussing the action of antimony on the liver it should be remembered that bilharzia itself destroys the liver cells by cirrhosis, and it would appear that the toxic dose of antimony for the parasite approaches very near the toxic doses for the liver cell: the margin of safety between the two is not a wide one. (I am speaking of individual doses. Antimony being eliminated quickly by the kidneys and other organs not tending to accumulate in the tissues of the body.)

It may be asked: "Does the antimony produce a hepatic toxin lethal to the parasites which, in larger quantities, is toxic to the human organism?"

I have always favoured the theory of direct toxic action of the antimony on the parasite. This is, however, not universally agreed on, other workers favouring the indirect action theory, that is that the tissues produce a body lethal to the parasite—and it would appear possible that the liver cell furnishes the toxin which kills the parasite from the disordered protein metabolism. My own opinion is that the liver cell does not furnish the parasite toxin, for the parasite is not killed off in those cases in which intolerance is shown.

More work on the means of combating antimony intolerance in bilharziasis is necessary.

Symptoms occurring during Intravenous Administration of Antimony Tartrate for Bilharziasis in Children.

It is usual to give a list of the symptoms, some or any of which may occur in children during the injection of antimony tartrate in the treatment of bilharziasis, somewhat in the following order:—

Cough, vomiting, nausea, dizziness, abdominal distress, diarrhœa, faintness, sudden death. This appears to me to be a mere list, beginning with cough and ending with sudden death.

It would seem better to classify, for these symptoms are not all equally important. Cough is the most common and the earliest, and is most marked in children: it occurs immediately after the injections and may be painful and distressing. It is

14 The exception which appears to prove my assertion is: Faust, Meleny, Hassell (1925), "A Study of Intensive Antimony Therapy in Schistosomiasis japonica," *Journ. Trop. Med. and Hyg.*, xxviii, 153.

15 "The biochemical action of intravenous antimony tartrate injections," J. B. Christopherson and S. Roodhouse Gloyne, *Lancet*, 1926 (i), 227.

16 H. B. Day—two such cases of jaundice occurred in his series of 1,000 cases treated by antimony tartrate, *Lancet*, 1921 (i), 525.

17 Faust, E. C., and Meleny, H. E., "Studies on Schistosomiasis japonica," mention jaundice and acute liver disturbances as contra-indications against antimony administration, *Amer. Journ. of Hyg.*, Mon. Series, No. 3, 1924.

not in itself dangerous, but when severe, indicates a reduction in the single dose. A metallic taste in the mouth, a dry feeling in the larynx, are common; a feeling of nausea or vomiting may occur, again chiefly in children. Abdominal pain and a little diarrhœa, or the passage of a large quantity of urine; some dizziness, are sometimes complained of. All of these may be regarded as useful signs which call for regulation of the dosage of antimony: they indicate the response of the various mucous or other membranes to the antimony as it circulates in the blood. There are other symptoms which are of much more importance. They do not occur immediately after the injection, but may occur within half an hour. Faintness, pallor, signs of shock, wiry pulse, shallow breathing, dusky lips, dilated pupils, cold extremities, headache, etc., all allergic signs, serious, requiring prompt treatment—namely, hot water bottles, blankets, drying the skin, rubbing the extremities, the administration of a little dilute warm brandy or the hypodermic administration of brandy, adrenalin, digitalin. These signs indicate, I believe, hepatic intolerance,[18] and remedies to combat them should be at hand. Later, within twelve hours, come the severe muscular pains, frequent in adults, which indicate also that the metabolism of the liver is disturbed. They may necessitate the reduction of the dose by reason of their severity, but they do not call for suspension of the drug. I am inclined to think that these muscular pains, which are painful and paralysing, occur in alcohol-drinking rather than abstaining nations. A rise of temperature sometimes occurs in antimony administration—the actual cause is not clear. In a case of a girl aged 9 (after enteric), the temperature rose to 105° F.

Finally it must be remembered that some of the toxic symptoms, in the early days attributed to antimony, were due to drug impurities, especially arsenic and lead (Khalil).

Much of the antimony given at the beginning of the revival of the use of the drug was old. Antimony had not been in active use for many years. Many-years-old stocks were brought out and used. This has now been rectified. Antimony is much more carefully prepared than before, dispensing is more accurate, tablets made by well-known wholesale chemists have largely replaced solutions made up by local dispensers.

To sum up.—Symptoms due to stimulation of mucous membranes of organs in the blood-vessels of which the antimony is circulating, should be carefully distinguished from more serious symptoms due to the interference of the metabolism of an important organ such as the liver. The former are not dangerous; they are even useful, as signals to regulate the single dose. It should be remembered that the organ to be feared in injection of tartar emetic is the liver, and only the liver, provided the now well-known therapeutic doses are not exceeded.

Fixing the dosage of antimony for children.—Writers on the treatment of bilharzia disease favour several methods: (1) Calculation according to the weight of the child. This method is highly recommended by many and practised by none. 0·002 grammes for every kilo body-weight are the figures usually quoted, and this works out at about 2 gr. for the average man of 10 st.

Two grains cannot be said to be wrong for a man weighing 10 st., but half of this (gr. i) is not necessarily the maximum dose for a boy aged 10 years who weighs about 5 st.

(2) Calculation according to age: This also is a purely empirical method—children of the same age differ so much in robustness and weight. The age method is therefore misleading.

(3) Calculation according to weight and age combined: This is a better method than calculating by either separately.

Methods appropriate to laboratory animals are not, however, practicable in fixing the dosage for human beings.

[18] Other signs of hepatic intolerance which may show themselves later are jaundice and bilious vomiting. They are not very frequent.—J. B. C.

For practical purposes it is necessary to have a simple working plan. In giving antimony to children in bilharziasis, the aim as with adults is to give the largest tolerated dose in order to kill the parasite, but the dose required to kill the parasite in children comes very near the largest dose tolerated by the liver cell; indeed, sometimes the largest dose which the liver cell will tolerate is not sufficient to kill the parasite. There is only one way of finding the appropriate dose: it is to commence with a dose which we know the liver cell will tolerate, inject every other day, increasing each injection by a small increment until the maximum dose is reached, and then continue with this maximum until the course is completed,[19] and the worms are killed. Antimony tartrate is a drug whose administration must be left to the skill and judgment of only careful administrators, and should never be in the hands of empirics.

Nationality, age, general condition, the presence of concurrent disease and idiosyncrasy, all should have a share of consideration in determining the dosage of antimony tartrate, because the parasitotropic approaches closely to the organotropic dose. Concurrent diseases should be treated before the antimony course is commenced, and it should be remembered that patients with heavy infections of bilharzia disease are more tolerant of antimony than persons with lighter infections or with no infection at all. My experience has led me to believe that if the toxic dose for the liver cell is reached, that is, if allergic symptoms once appear, the patient becomes sensitized, as it were, to antimony, and it is of little use proceeding. This especially applies to children. This sensitization may be due to too cautious or to too rapid attempts to reach the parasiticidal dose. It is necessary always in children to take notice of symptoms which, though they are not symptoms of antimony poisoning, indicate antimony sensibility, namely, cough, a feeling of nausea, vomiting, diarrhœa, etc. When they occur the dose should not be increased. I have studied the writings of workers who have had most clinical experience of bilharziasis in children —H. B. Day, J. G. Bateman and colleagues in Cairo, F. G. Cawston in Durban, also the excellent Instructions for the School Bilharzia Clinics of the Transvaal, especially organized to carry out the treatment of children. In spite of the limitation of this South African pamphlet, which deals only with children between the ages of 8 and 12, it gives valuable information. Healthy children between the ages of 12 and 16 may commence with gr. $\frac{1}{2}$ with increases of gr. $\frac{1}{4}$ on alternate days, and continue the maximum dose of gr. $1\frac{1}{2}$ on alternate days till the full course of 20 to 25 gr. is reached. The total dose is a matter of judgment; a healthy boy of 16 may be given 25 gr. The ordinary child, aged from 8 to 12, commences with gr. $\frac{1}{4}$ with increases of gr. $\frac{1}{4}$ on alternate days to the maximum of gr. 1 and a total of gr. 20 for 12 years of age, and lesser total amounts for the younger patients. It is not easy to inject children between the ages of 4 and 7 years at all, though sometimes hand veins and foot veins can be utilized, but if suitable veins can be found, the commencing dose of gr. $\frac{1}{4}$ would be appropriate, with increases of gr. $\frac{1}{8}$ on alternate days to a maximum of gr. 10.

In the case of young children whose veins cannot be utilized, emetine, gr. $\frac{1}{2}$ daily, may be given intramuscularly, or colloidal antimony, 2 c.c., as recommended by H. B. Day (*Lancet*, 1921, (i), 525). It should be remembered that larger doses of emetine are required in bilharziasis than in amœbic dysentery; the heart should therefore be carefully watched during the administration of emetine.

Fouadin, a trivalent organic synthetic compound (neo-antimosan) is now on trial. It may prove useful in the treatment of bilharziasis in children and in debilitated persons. It is painless and is used intramuscularly, and stated to be non-toxic. Like all synthetic organic compounds it is too expensive for mass treatment. The pentavalent organic preparations of antimony are useless in bilharzia disease—they are non-toxic both to host and parasite.

[19] Certain facts appear to point to a danger of the liver cell becoming sensitized to antimony tartrate by a too cautious procedure at the beginning of the course.—J. B. C.

Antimony tartrate in very large doses *per rectum* for children was advocated by H. Wilson in Northern Rhodesia, but it has been abandoned. It may just be mentioned that antimony tartrate given intraperitoneally has been suggested for infants.

Emetine periodide by mouth has been tried by R. M. Gordon with some success (*Ann. Trop. Med. and Paras.*, 1926, xx, 229), gr. i three times daily for fifteen days. I have had no experience of the drug. It is expensive.

Finally, there is a method of dealing with bilharziasis in children whose veins cannot be found for intravenous injection. Leave the case for a year or so and in the meantime, by periodically stroking the arm in the direction of the venous flow, endeavour to make the veins more prominent. Bilharziasis in children does not always call for immediate treatment.

The treatment of bilharziasis in children entails much individual judgment and skill on the part of the doctor and nurses—qualities which can be acquired with practice by missionary workers and native orderlies in hospitals, institutions and clinics in bilharzia-infected countries in Africa.

Discussion.—Dr. N. HAMILTON FAIRLEY said that in applying tartar emetic treatment to schistosomiasis, Dr. Christopherson had made a great contribution to therapeutics, and he stressed what was equally important and sometimes forgotten, namely, the necessity for prolonged courses of the treatment and the pushing of the drug to its physiological limits to get optimum benefit. Deleterious effects of treatment such as those described by Dr. Christopherson were relatively rare considering the great number of cases treated by intravenous injections of antimony in tropical countries. He (the speaker) agreed that the liver might be affected adversely by antimony, but doubted whether the syndrome of pallor, vomiting, collapse, etc., sometimes caused by these intravenous injections, could be ascribed to allergy. Had sensitization developed in the interval between the first and second series of injections, the onset of symptoms would be expected to occur at the first injection of the second series, and not, as in Dr. Christopherson's cases, later in the administration of the drug. Granted, however, that a hypersensitive or anaphylactoid state did exist, then the mechanism of its production would, he thought, have differed from that described by Dr. Christopherson. If a saline extract of cercariæ or adult schistosomes was injected intradermally into a patient suffering from bilharziasis, a large urticarial wheal with pseudopodial outrunners developed at the site of inoculation. This wheal was indistinguishable from the wheal produced by the injection of histamine into a normal individual, and the brilliant researches of Lewis had indicated that wheal formation of this nature was dependent on the liberation of histamine or "H. substance" as the result of the linkage of antigen and antibody within the endothelial cells of the superficial vessels. In like manner, if allergic reactions occurred with visceral manifestations, as a result of tartar emetic treatment in schistosomiasis, a reasonable explanation would be that the drug was killing off the parasites in the portal circulation with the liberation of bilharzia antigen which would inevitably be filtered out in the liver and there unite with intracellular antibody liberating "H. substance" *in situ*. Such a conception would explain hepatic derangement in terms of modern views of immunity.

He (Dr. Fairley) remembered treating a Baghdad Mahommedan for vesicle bilharzia with intravenous injections of tartar emetic, and after the patient had received about 9 grams of antimony he had become severely ill with vomiting, low blood-pressure, marked pallor and diarrhœa, the picture resembling in its essential features that met with in Dr. Christopherson's two cases. Two days later, however, severe jaundice had developed, with bile-salts and bile-pigments in the urine. The patient was treated with stimulants, large quantities of fluid alkalies and glucose, and, after a very grave illness, he had gradually recovered. Undoubtedly the pathology of this condition was a toxic necrosis of the liver due to antimony administration, and its interest, so far as the present paper was concerned, lay in the fact that it merely represented a further stage in the development of toxic features. At its onset the symptoms resembled those described by Dr. Christopherson.

Dr. HUGH S. STANNUS said that the untoward symptoms described in the two children treated with antimony were comparable with those seen in some cases of syphilis treated with organic arsenicals, just as the case of jaundice, following the exhibition of antimony, mentioned by Dr. Fairley, resembled similar cases of arsenical jaundice. These symptoms

were, he believed, toxic manifestations, and not truly allergic in nature. The protective use of glucose had been mentioned in connection with poisons acting on the liver cells, but drachm doses given shortly before, or coincidentally with the administration of the drug, would probably be of little value. It was necessary to have the liver stocked with glycogen, and to this end four ounces of glucose some hours before would be more useful.

He would like to know whether other patients were treated with the same batch of antimony as the two children, without showing toxic symptoms.

In suggesting that the symptoms described were allergic phenomena, and due to action of the liver cells, Dr. Christopherson had argued rather from analogy and appeared to have brought forward little real evidence of upset of liver function in these cases.

Dr. CHRISTOPHERSON (in reply) said that some vagueness and obscurity existed in the use of the medical terms "allergy" and "allergic," and they needed clearer definition. They were used by him actually to denote the syndrome pallor, vomiting, collapse, etc., and not any specific cause for the symptoms. The action of histamine was analogous but not necessarily identical.

Dr. Fairley's suggestion that the so-called allergic symptoms might be caused by the killing off of the parasites with the liberation of the bilharzia antigen uniting with the intracellular antibody liberating "H. substance" *in situ*, appeared to be negatived by the fact that the same symptoms arose when the bilharzia worm was not present, namely, in rabbits experimentally poisoned by antimony tartrate. The explanation that this was due to the direct action of the antimony on the metabolism of the liver cell would seem to be unavoidable.

He agreed with Dr. Stannus that one drachm of glucose given with the antimony was not going to do much good. There was no convincing evidence so far that larger doses of glucose would obviate the allergic symptoms. No other patient had been treated with the same batch of antimony as the two children, but they had been treated with different batches of antimony tartrate with the same result. More evidence of the toxic action of antimony tartrate on the liver cell was given in the paper [which could not be read *in extenso*]. It would seem that antimony tartrate had a specific toxic action on the liver cell—as it had on the bilharzia organism, and in order to get the toxic action on the parasite it was necessary to approach the dose toxic to the liver cell; therein lay the danger.